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Dennis G. Hall

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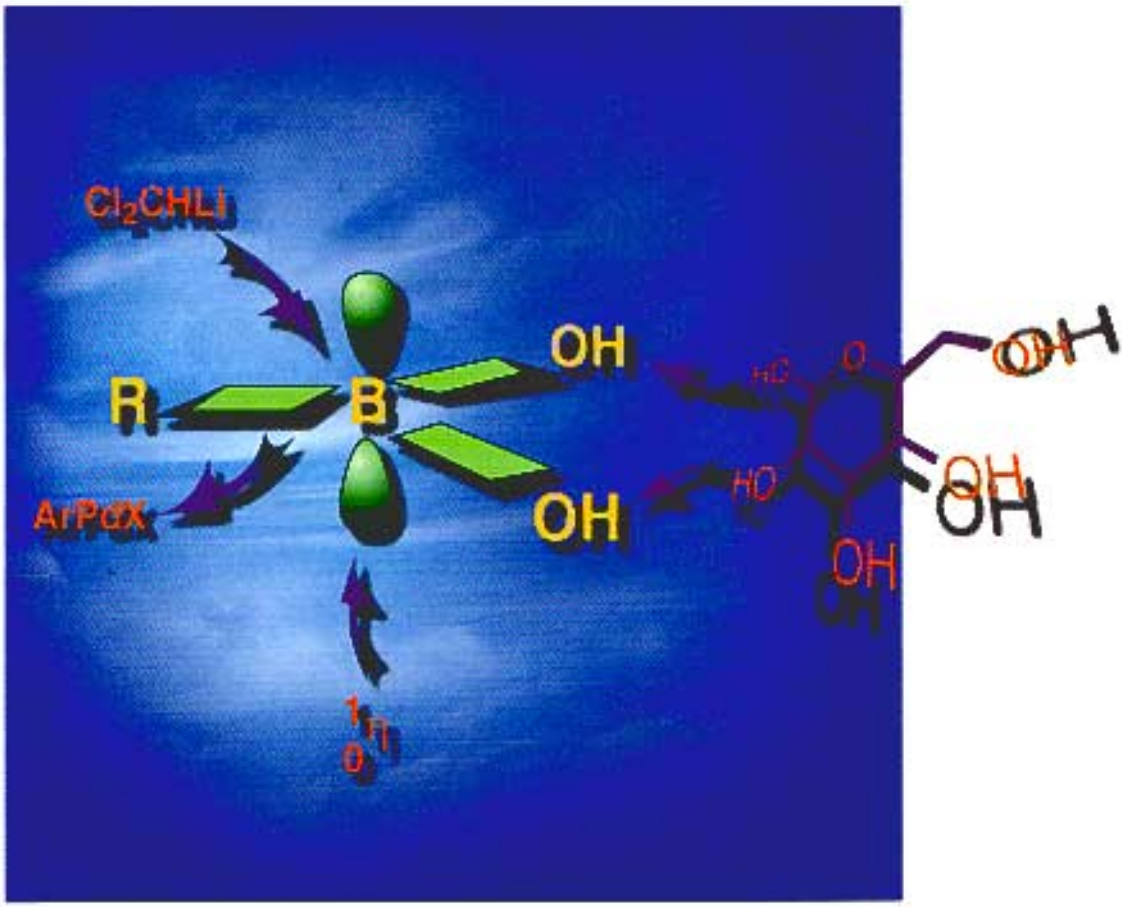
Boronic Acids

Preparation, Applications in
Organic Synthesis and Medicine



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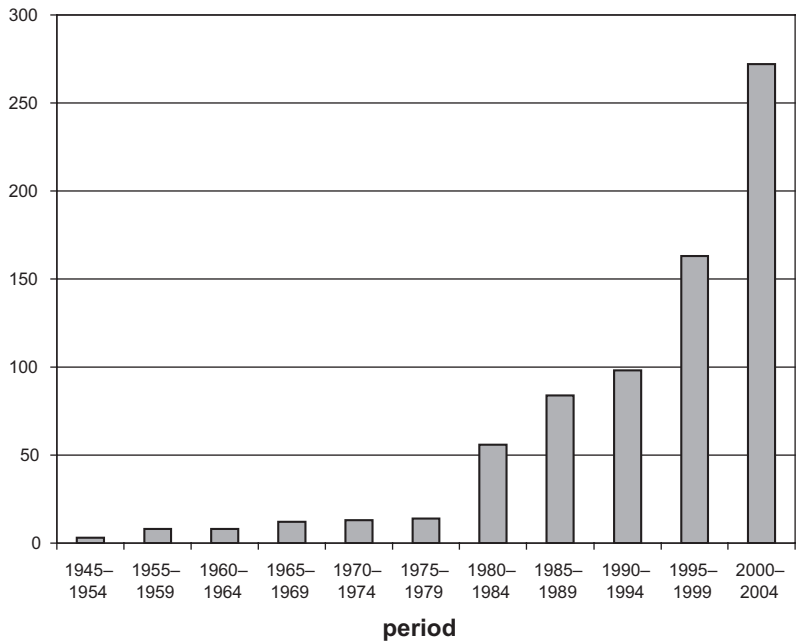
Preface

From the first isolation of a boronic acid by Frankland in 1860 to the report of their palladium-catalyzed cross-coupling with carbon halides by Suzuki and Miyaura in 1979, advances in the chemistry and biology of boronic acids have been few and far between. The early 1980's announced a drastic turn. In the past decade alone, numerous breakthroughs have been reported. From the discovery of rhodium-catalysed couplings with alkenes and aldehydes to the commercialisation of Velcade®, the first boronic acid drug used in human health therapy, new applications of boronic acids have been reported at a spectacular rate. As seen on the histogram below, the number of publications focused on boronic acid derivatives has increased exponentially, elevating boronic acids to a new status, that of a prized class of organic compounds.



Histogram. Number of publications focused on boronic acids over time (Note that only those publications including the word "boronic" in their title were included).

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This sudden rise in the usefulness and popularity of boronic acids necessitated a comprehensive book on their chemistry and biology. In just a few years working in the field of boronic acid chemistry, I had quickly come to regret the absence of a specialised book on this topic. Thus, I could not turn down an opportunity to help fulfill this need and lead such a project. I was most fortunate to assemble a select group of experts that literally includes legends in the field. The result is a book containing 13 chapters that cover all modern aspects of boronic acid derivatives. All efforts were made to achieve comprehensive coverage of the literature up to 2004, with particular emphasis on topics of great interest to a large audience of synthetic organic, organometallic, and medicinal chemists.

Our current understanding of the structure and properties of boronic acids, their important ester derivatives and other parent compounds like trifluoroborate salts, is described in Chapter 1. The limited number of methods for the preparation of boronic acid derivatives had long impeded their use as synthetic reagents. The outlook is changing rapidly, however, and Chapter 1 describes modern methods for the preparation of all types of boronic acid derivatives, with several useful tables of examples. It also provides an overview of their synthetic, biological, and medicinal applications. One of the latest advances in the preparation of boronic acids, the use of C-H activation/borylation methods, is discussed in Chapter 2. Much has happened in the development of new conditions and catalysts to expand the scope of transition metal catalysed C-C bond formation processes using boronic acids. Chapter 3 describes the most recent advances in the Suzuki cross-coupling between aromatic boronic acids and aromatic halides. A few years ago, rhodium(I) complexes were found to catalyse the addition of boronic acids to enones and aldehydes. These discoveries have now flourished into highly efficient catalytic enantioselective processes that can afford functionalyzed products in over 99% optical purity. All the details of such impressive advances are reviewed in Chapter 4. The copper-catalysed coupling of boronic acids with heteroatom functionalities like phenols, amines, and amides is yet another recent synthetic application that has contributed to the recent emergence of boronic acids as a popular class of reagents. This new and useful process, described in Chapter 5, has become firmly established in natural product synthesis and medicinal chemistry research. Already a workhorse in the synthesis of polypropionate compounds, the addition of allylboronates to carbonyl compounds is still getting increasing attention as a result of recent improvements in the preparation of functionalised allylboronates. These new preparative methods and other advances such as the Lewis acid-catalysed allylboration and tandem processes are described in Chapter 6. The important discovery that boronic acids add to imine derivatives and iminium ions, even in a three-component fashion, has been exploited in a number of synthetic applications and progress in this area is reviewed for the first time in Chapter 7. Described in Chapter 8 is the chemistry of alpha-haloalkyl boronic esters, including the seminal Matteson homologation, which has led to a rich field of asymmetric synthesis with applications to the construction of complex natural products and to the preparation of alpha-aminoalkyl boronic acids employed as enzyme inhibitors. Another important area of investigation focuses on the use of unsaturated boronic esters in a wide variety of electrophilic additions and cycloadditions. As described in

Chapter 9, the new boronic acid products of these reactions can be exploited further by making use of the numerous possibilities of transformations offered by the residual boronate group. Boronic acids and several of their ester derivatives can serve as stable and mild Lewis acids, and this unique property has inspired the development of catalysts for several reaction processes, including asymmetric transformations; this topic is reviewed in Chapter 10. Likewise, the use of chiral oxazaborolidines in the asymmetric reduction of ketones and imine derivatives is described in Chapter 11. The ability of boronic acids to form reversible covalent adducts with the diol units of carbohydrates has been exploited in the development of receptors for saccharides. Of particular interest is the development of sensors to measure the blood glucose level of diabetes patients, and a comprehensive review of this intensive area of research is presented in Chapter 12. Boronic acids have long been known to bind and inhibit the action of certain classes of proteolytic enzymes. This important topic, as well as the potential of boronic acids as boron neutron capture agents, is discussed in Chapter 13 along with other emerging therapeutic applications. From the rich contents of this book, it is clear that the spectacular rise of popularity of boronic acids as a class of compounds may have just begun. It is hoped that this first comprehensive monograph on boronic acids will contribute to generating more work and attract more researchers to the field.

The success of a book project relies heavily on the involvement of several dedicated individuals. I would like to thank all authors and co-authors who have generously agreed to contribute a chapter. Their expert participation and professionalism was an invaluable asset to this ambitious project. Grateful acknowledgements are also offered to the Wiley-VCH editorial staff, in particular to Elke Maase and Renate Doetzer. For their valued support in various stages of editing this book I am also indebted to Hugo Lachance, Barry Touré, Duane Stones, Siu Hong Yu, Vivek Rauniyar, Lisa Carosi, Meena Dowlut, Agnieszka Ulaczyk-Lesanko, Diane Burke, Tim Elford, Xuri Gao, Feng Peng, and Annie Tykwinski (Book cover).

Edmonton (Alberta), March 2005 *Dennis Hall*

1
Structure, Properties, and Preparation Of Boronic Acid Derivatives. Overview of Their Reactions and Applications

Dennis G. Hall

1.1
Introduction

Structurally, boronic acids are trivalent boron-containing organic compounds that possess one alkyl substituent (i.e., a C–B bond) and two hydroxyl groups to fill the remaining valences on the boron atom (Figure 1.1). With only six valence electrons and a consequent deficiency of two electrons, the sp^2-hybridized boron atom possesses a vacant p orbital. This low-energy orbital is orthogonal to the three substituents, which are oriented in a trigonal planar geometry. Unlike carboxylic acids, their carbon analogues, boronic acids are not found in nature. These abiotic compounds are derived synthetically from primary sources of boron such as boric acid, which is made by the acidification of borax with carbon dioxide. Borate esters, the main precursors for boronic acid derivatives, are made by simple dehydration of boric acid with alcohols. The first preparation and isolation of a boronic acid was reported by Frankland in 1860 [1]. By treating diethylzinc with triethylborate, the highly air-sensitive triethylborane was obtained, and its slow oxidation in ambient air eventually provided ethylboronic acid. Boronic acids are the products of the second oxidation of boranes. Their stability to atmospheric oxidation is considerably superior to that of borinic acids, which result from the first oxidation of boranes. The product of a third oxidation of boranes, boric acid, is a very stable and a relatively benign compound to humans (Section 1.2.2.3).

Their unique properties as mild organic Lewis acids and their mitigated reactivity profile, coupled with their stability and ease of handling, makes boronic acids a particularly attractive class of synthetic intermediates. Moreover, because of their low toxicity and their ultimate degradation into the environmentally friendly boric acid, boronic acids can be regarded as "green" compounds. They are solids that tend to exist as mixtures of oligomeric anhydrides, in particular the cyclic six-membered boroxines (Figure 1.1). For this reason and other considerations outlined below, the corresponding boronic esters are often preferred as synthetic intermediates. Although other classes of organoboron compounds have found tremendous utility in organic

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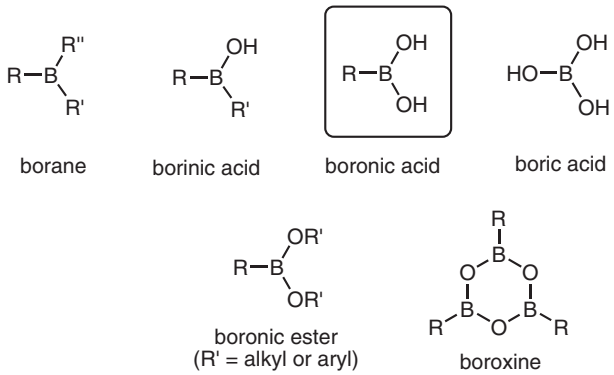


Figure 1.1 Oxygenated organoboron compounds.

synthesis, this book focuses on the most recent applications of the more convenient boronic acid derivatives. For a comprehensive description of the properties and reactivity of other classes of organoboron compounds, interested readers may refer to a selection of excellent monographs and reviews by Brown [2], Matteson [3], and others [4–7]. In the past two decades, the status of boronic acids in chemistry has risen from peculiar and rather neglected compounds to a prime class of synthetic intermediates. Much progress, described in hundreds of publications, has happened since the last review on boronic acid chemistry by Torssell in 1964 [8]. For instance, hopes for boronic acid based therapeutics have finally concretized [9]. The recent approval of the anti-cancer agent Velcade®, the first boronic acid containing drug commercialized (Section 1.6.5), further confirms the new status of boronic acids as an important class of compounds in chemistry and medicine. This chapter describes the structural and physicochemical properties of boronic acids and their many derivatives, as well as their methods of preparation. A brief overview of their synthetic and biological applications is presented, with an emphasis on topics not covered in other chapters.

1.2
Structure and Properties of Boronic Acid Derivatives

1.2.1
General Types and Nomenclature of Boronic Acid Derivatives

The reactivity and properties of boronic acids is highly dependent upon the nature of their single variable substituent; more specifically, by the type of carbon group (R) directly bonded to boron. In the same customary way as for other functional groups, boronic acids are classified conveniently in subtypes such as alkyl-, alkenyl-, alkynyl-, and aryl- boronic acids.

When treated as an independent substituent, the prefix borono is employed to name the boronyl group (e.g., 3-boronoacrolein). For cyclic derivatives such as boronic esters, the IUPAC RB-1-1 rules for small heterocycles (i.e., the Hantzsch–Widman system) are employed along with the prefix "boro". Thus, saturated five- and six-membered cyclic boronic esters are, respectively, named as dioxaborolanes and dioxaborinanes. For example, the formal name of the pinacol ester of phenylboronic acid is 2-phenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The corresponding nitrogen analogues are called diazaborolidines and diazaborinanes , and the mixed nitrogen–oxygen heterocycles are denoted by the prefix oxaza. Unsaturated heterocycles are named as boroles.

1.2.2 Boronic Acids

1.2.2.1 Structure and Bonding

The X-ray crystal structure of phenylboronic acid (**1**, Figure 1.2) was reported in 1977 by Rettig and Trotter [10]. The crystals are orthorhombic, and each asymmetric unit consists of two distinct molecules, bound through a pair of O–H---O hydrogen bonds (A and B, Figure 1.3). The CBO_2 plane is quite coplanar with the benzene ring, with a respective twist around the C–B bond of 6.6°and 21.4° for the two independent molecules of $PhB(OH)_2$. Each dimeric ensemble is also linked with hydrogen bonds to four other similar units to give an infinite array of layers (C, Figure 1.3). X-ray crystallographic analysis of other arylboronic acids like *p*-methoxyphenyl boronic acid (**2**) [11] and 4-carboxy-2-nitrophenyl boronic acid (**3**, Figure 1.2) [12] are consistent with this pattern. Recently, the structures of two heterocyclic boronic acids, 2-bromo- and 2-chloro- 5-pyridylboronic acids (**4** and **5**), were reported [13].

Whereas the boronic acid group has a trigonal geometry and is fairly coplanar with the benzene ring in structures **1**and **2**, and **4** and **5**, it is almost perpendicular to the ring in **3**. This is likely due to a combination of two factors: minimization of steric strain with the ortho-nitro group, and also because of a possible interaction between one oxygen of the nitro group and the trigonal boron atom. Inspired by the structur-

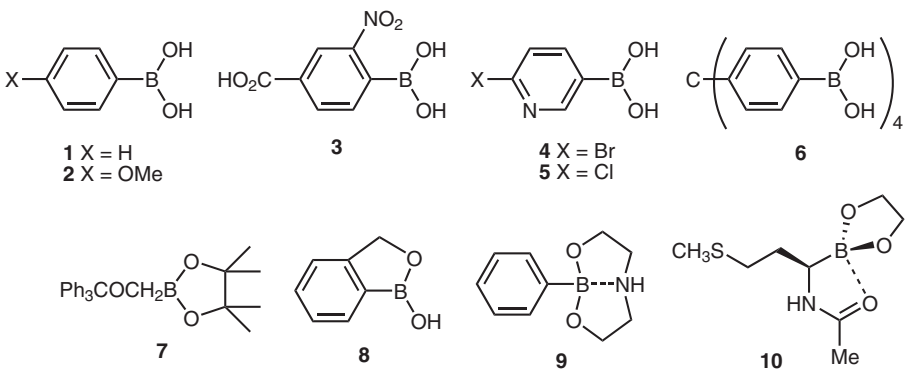


Figure 1.2 Boronic acid derivatives analyzed by X-ray crystallography.

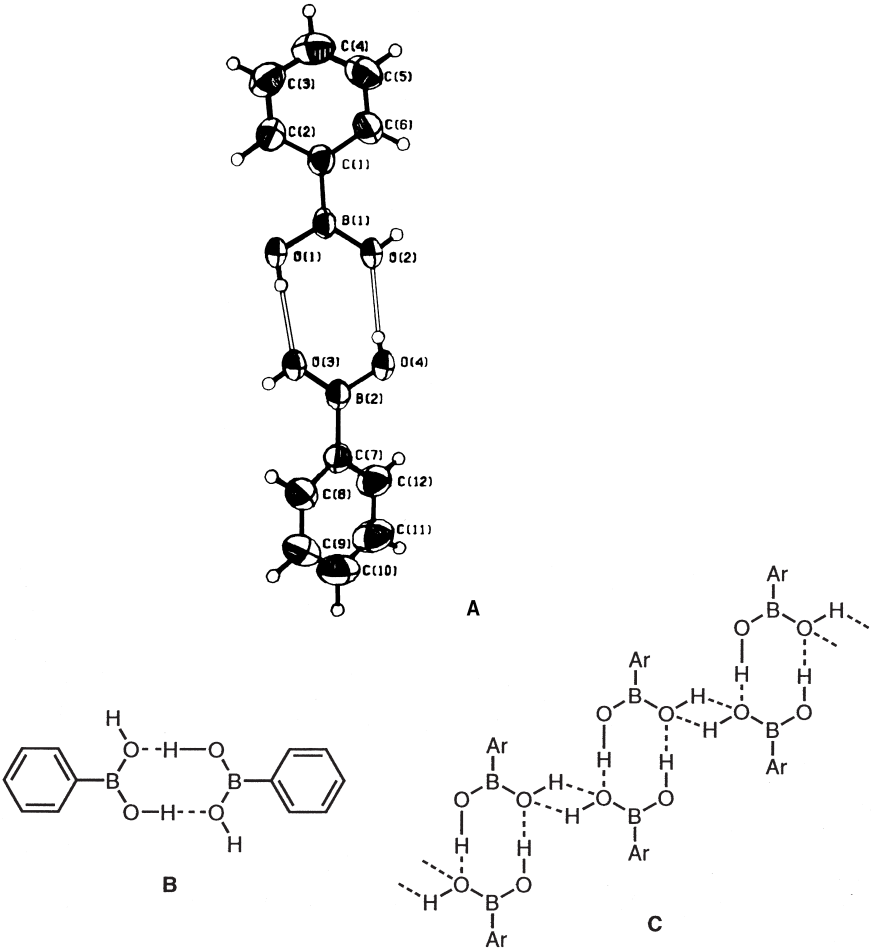


Figure 1.3 Representations of the X-ray crystallographic structure of phenylboronic acid. (A) ORTEP view of a dimeric unit. (B) Dimeric unit showing hydrogen bonds. (C) Extended hydrogen-bonded network.

al behavior of phenylboronic acid and its propensity to form hydrogen-bonded dimers, Wuest and co-workers recently reported the design of new diamond-like porous solids from the crystallization of tetrahedral-shaped tetraboronic acid **6** (Figure 1.2) [14]. Recently, phenyl- and *p*-methoxyphenyl boronic acids were found to co-crystallize with 4,4′-bipyridine into similar supramolecular assemblies involving hydrogen bonds between $B(OH)_2$ groups and the bipyridine nitrogens [15]. With a range of approximately 1.55–1.59 Å, the C–B bond of boronic acids and esters is slightly longer than typical C–C single bonds (Table 1.1). The average C–B bond energy is also slightly less than that of C–C bonds (323 vs. 358 kJ mol^{-1}) [16]. Consistent with strong B–O bonds, the B–O distances of tricoordinate boronic acids such as

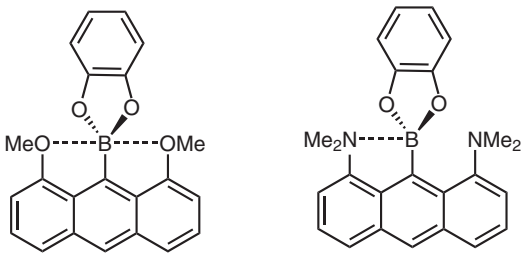
phenylboronic acid are fairly short, and lie in the range 1.35–1.38 Å (Table 1.1). These values are slightly larger than those observed in boronic esters. For example, the B–O bond distances found in the X-ray crystallographic structures of trityloxymethyl pinacolate boronic esters (e.g., **7** in Figure 1.2) are in the range 1.31–1.35 Å (Table 1.1), and the dioxaborolane unit of these derivatives is nearly planar [17]. The X-ray crystallographic structure of cyclic hemiester **8** (Figure 1.2) has been described [18]. Like phenylboronic acid, this compound also crystallizes as a hydrogen-bonded dimer; however, without the extended network because of the absence of a second hydroxyl group. The cyclic nature of this derivative induces a slight deviation from planarity for the tricoordinate boronate unit, as well as a distortion of the bond angles. The endocyclic B–O bond in **8** is slightly longer than the B–OH bond. This is attributed to the geometrical constraints of the ring, which prevents effective lone pair conjugation between the endocyclic oxygen and the vacant orbital of boron.

To complete boron's octet, boronic acids and their esters may also coordinate basic molecules and exist as stable tetracoordinated adducts. For example, the X-ray crystallographic structure of the diethanolamine adduct of phenylboronic acid (**9**, Figure 1.2), which was also reported by Rettig and Trotter [19], confirmed the transannular B–N bridge long suspected from other spectroscopic evidence such as NMR [20, 21]. This dative B–N bond is 1.67 Å long (Table 1.1). This interaction induces a strong $N^{\delta+}$–$B^{\delta-}$ dipole that points away from the plane of the aryl ring – an effect that was elegantly exploited in the design of a diboronate paraquat receptor [22]. When tetracoordinated, such as in structures **9** or **10** [23] (Figure 1.2), the B–O bond of boronic esters increases to about 1.43–1.47 Å, which is as much as 0.10 Å longer than the corresponding bonds in tricoordinate analogues (Table 1.1). These markedly longer B–O bonds are comparable to normal C–O ether linkages (~1.43 Å). These comparisons emphasize the considerable strength of B–O bonds in trigonal boronic acid derivatives. This bond strength originates from conjugation between the lone pairs on the oxygens and boron's vacant orbital, which confers partial double bond character to the B–O linkage. It was estimated that formation of tetrahedral adducts (e.g., with NH_3) may result in a loss of as much as 50 kJ mol^{-1} of B–O bond energy compared to the tricoordinate boronate [24]. Not surprisingly, trigonal B–O bonds are much stronger than the average C–O bonds of ethers (519 vs. 384 kJ mol^{-1}) [16].

Table 1.1 Bond distances from X-ray crystallographic data for selected boronic acid derivatives (Figure 1.2).

Compound	B–C (Å)	B–O^1 (Å)	B–O^2 (Å)	B–X (Å)	Reference
1	1.568	1.378	1.362	–	10
2	1.556	–	–	–	11
3	1.588	1.365	1.346	–	12
4	1.573	1.363	1.357	–	13
5	1.573	1.362	1.352	–	13
7	1.560	1.316	1.314	–	17
8	1.494	1.408	1.372	–	18
9	1.613	1.474	1.460	1.666	19
10	1.613	1.438	1.431	1.641	23

In rare instances where geometrical factors allow it, boronic acid derivatives may become hypervalent. For example, catechol ester **11** (Figure 1.4) was found by X-ray crystallographic analysis to be pentacoordinated in a highly symmetrical fashion as a result of the rigidly held ether groups, which are perfectly positioned to each donate lone pair electrons to both lobes of the vacant p orbital of boron [25]. The boronyl group of this two-electron three-atom center is planar, in a sp^2 hybridization state, and the resulting structure has a slightly distorted trigonal bipyramidal geometry. The corresponding diamine **12**, however, behaved quite differently and demonstrated coordination with only one of the two NMe_2 groups [26].



11 **12**

Figure 1.4 Model compounds for boronate hypercoordination.

Due to electronegativity differences (B = 2.05, C = 2.55) and notwithstanding the electronic deficiency of boron, which is mitigated by the two electron-donating oxygen atoms (vide supra), the inductive effect of a boronate group should be that of a weak electron-donor. The ^{13}C NMR alpha effect of a boronate group is very small [27]. Conversely, the deficient valency of boron and its relatively similar size to carbon has long raised the intriguing question of possible pi-conjugation between carbon and boron in aryl- and alkenylboronic acids and esters [28]. NMR data and other evidence like UV and photoelectron spectroscopy, and LCAO-MO calculations, suggest that B–C conjugation occurs to a modest extent in alkenylboranes [29–31], and is probably minimal for the considerably less acidic boronate derivatives. A thorough comparative study of ^{13}C NMR shift effects, in particular the deshielding of the beta-carbon, concluded to a certain degree of mesomeric pi-bonding for boranes and catecholboronates [27]. For example, compared to analogous aliphatic boronates, the beta-carbons of a dialkyl alkenylboronate and the corresponding catechol ester are deshielded by 8.6 and 18.1 ppm respectively. In all cases, the beta-carbon is more affected by the boronate substituent than the alpha-carbon, which is consistent with some contribution from the B–C π-bonding form (B) to give resonance hybrid C (Figure 1.5). X-Ray crystallography may also provide clues on the extent of B–C π-bonding. The B–C bond distances for arylboronic acids (Table 1.1) differ enough to suggest a small degree of B–C π-bonding. The B–C bond distance (1.588 Å) in the electron-poor boronic acid **3**, which is incapable of π-conjugation because its vacant p orbital is orthogonal to the π-system of the phenyl ring, is expectedly longer than that of phenyl-

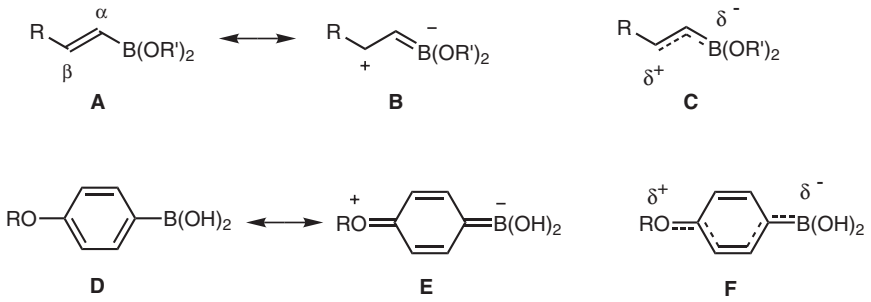


Figure 1.5 Limit mesomeric forms involving B–C π overlap.

boronic acid (1.568 Å). Interestingly, the B–C bond of **2** is 1.556 Å long, suggesting only a minimal contribution from the mesomeric form E (Figure 1.5).

Conversely, the B–C bond (1.613 Å) in the diethanolamine adduct **9** (Table 1.1), where the boron vacant orbital is also incapacitated from B–C overlap, is 0.045 Å longer than that of free phenylboronic acid (**1**). In so far as bond length data correlates with the degree of π-bonding [32], this comparison is consistent with a small B–C π-bonding effect in arylboronic acids and esters (i.e., hybrid form F in Figure 1.5). This view is further supported by chemical properties such as substituent effects on the acidity of arylboronic acids (Section 1.2.2.4.1) and ^{11}B chemical shifts correlations [33]. Likewise, B–C π-bonding in alkenylboronic acids and esters should be significant, but this effect must be weak compared to the electron-withdrawing effect of a carbonyl or a carboxyl group. For instance, alkenylboronic esters do not readily act as Michael acceptors with organometallic reagents in the same way as unsaturated carbonyl compounds [34]. Yet, the formal electron-withdrawing behavior of the boronate group seems undeniable, as shown by the reactivity of dibutylethylene boronate in cycloadditions with ethyldiazoacetate [35] and in Diels–Alder reactions where it provides cycloadducts with dienes like cyclopentadiene [36] and cyclohexadiene, albeit only at elevated temperatures (ca. 130 and 200 °C respectively) [37, 38]. The behavior of ethylene boronates as dienophiles has been rationalized by MO calculations [28], but their reactivity stands far from that of acrylates in the same reaction. In fact, more recent high level calculations suggest that the reactivity of alkenylboronates in Diels-Alder reactions may be due more to a three-atom-two-electron center stabilization of the transition state rather than a true LUMO-lowering electron-withdrawing mesomeric effect from the boronate substituent [39]. Further evidence for the rather weak electron-withdrawing character of boronic esters comes from their modest stabilizing effect in boronyl-substituted carbanions, where their effect has been compared to that of a phenyl group (Section 1.3.8.3).

1.2.2.2 **Physical Properties and Handling**

Most boronic acids exist as white crystalline solids that can be handled in air without special precautions. At ambient temperature, boronic acids are chemically stable and most display shelf-stability for long periods (Section 1.2.2.5). They do not tend to dis-

proportionate into their corresponding borinic acid and boric acid even at high temperatures. To minimize atmospheric oxidation and autoxidation, however, they should be stored under an inert atmosphere. When dehydrated, either with a water-trapping agent or through co-evaporation or high vacuum, boronic acids form cyclic and linear oligomeric anhydrides such as the trimeric boroxines (Figure 1.1). Fortunately, this is often inconsequential when boronic acids are employed as synthetic intermediates. Many of their most useful reactions (Section 1.5), including the Suzuki cross-coupling, proceed regardless of the hydrated state (i.e., free boronic acid or boronic anhydride). Anhydride formation, however, may complicate analysis and characterization efforts (Section 1.4.3). Furthermore, upon exposure to air, dry samples of boronic acids may be prone to decompose rapidly, and boronic anhydrides were proposed as initiators of the autoxidation process [40]. For this reason, it is often better to store boronic acids in a slightly moist state. Incidentally, commercial samples tend to contain a small percentage of water that helps in their long-term preservation. Due to their facile dehydration, boronic acids tend to provide somewhat unreliable melting points (Section 1.4.3.1). This inconvenience, and the other above-mentioned problems associated with anhydride formation, largely explain the popularity of boronic esters as surrogates of boronic acids (Section 1.2.3.2).

The Lewis acidity of boronic acids and the hydrogen bond donating capability of their hydroxyl groups combine to lend a polar character to most of these compounds. Although the polarity of the boronic acid head can be mitigated by a relatively hydrophobic tail as the boron substituent, most small boronic acids are amphiphilic. Phenylboronic acid, for instance, has a benzene–water partition ratio of 6 [41]. The partial solubility of many boronic acids in both neutral water and polar organic solvents often complicates isolation and purification efforts (Section 1.4).

1.2.2.3 **Safety Considerations**

As evidenced by their application in medicine (Chapter 13), most boronic acids present no particular toxicity compared to other organic compounds [42]. Small water-soluble boronic acids demonstrate low toxicity levels, and are excreted largely unchanged by the kidney [43]. Larger fat-soluble boronic acids are moderately toxic [43–45]. Boronic acids present no particular environmental threat, and the ultimate fate of all boronic acids in air and aqueous media is their slow oxidation into boric acid. The latter is a relatively innocuous compound, and may be toxic only under high daily doses [46]. A single acute ingestion of boric acid does not even pose a threatening poisoning effect in humans [47] unless it is accompanied by other health malfunctions such as dehydration [48].

1.2.2.4 **Acidic Character**

By virtue of their deficient valence, boronic acids possess a vacant p orbital. This characteristic confers them unique properties as mild organic Lewis acids that can coordinate basic molecules. By doing so, the resulting tetrahedral adducts acquire a carbon-like configuration. Thus, despite the presence of two hydroxyl groups, the acidic character of most boronic acids is not that of a Brønsted acid (i.e., oxyacid) (Equation 1, Figure 1.6), but usually that of a Lewis acid (Equation 2). When coordinated

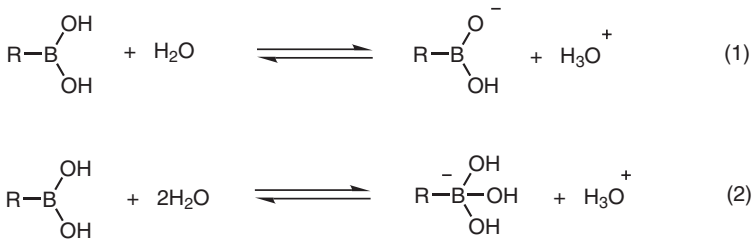


Figure 1.6 Ionization equilibrium of boronic acids in water.

with an anionic ligand, although the resulting negative charge is formally drawn on the boron atom, it is in fact spread out on the three heteroatoms.

1.2.2.4.1 Complexation Equilibrium in Water and Structure of the Boronate Anion

Although the acidic character of boronic acids in water had been known for several decades, the structure of the boronate ion (the conjugate base) was not elucidated until 1959. In their classical paper on polyol complexes of boronic acids [49], Lorand and Edwards demonstrated that the trivalent neutral form, likely hydrated, is in equilibrium with the anionic tetrahedral species (Equation 2, Figure 1.6), and not with the structurally related Brønsted base (i.e., the trivalent ion shown in Equation 1). It is this ability to ionize water and form hydronium ions by "indirect" proton transfer that characterizes the acidity of most boronic acids in water. Hence, the most acidic boronic acids possess the most electrophilic boron atom that can best form and stabilize a hydroxyboronate anion. The acidic character of boronic acids in water had been measured using electrochemical methods as early as the 1930s [50–52]. Phenylboronic acid, with a pK_a of 8.8 in water, is of comparable acidity to a phenol (Table 1.2). It is slightly more acidic than boric acid (pK_a 9.2). The pK_as of Table 1.2 show that the relative order of acidity for different types of boronic acids is aryl > alkyl. Bulky substituents proximal to the boronyl group were suggested to decrease the acid strength due to steric inhibition in the formation of the tetrahedral boronate ion. For example, ortho-tolylboronic acid is less acidic than its para isomer (pK_a 9.7 vs. 9.3, Table 1.2) [8]. This difference was explained in terms of F-strain in the resulting ion (Equation 3, Figure 1.7) [62], and this observation was taken as further evidence for the Lewis acidic behavior of boronic acids. As expected, electron-withdrawing substituents on the aryl group of arylboronic acids increase the acid strength by a fairly significant measure [50, 52, 55, 63]. For example, the highly electron-poor 3-methoxycarbonyl-5-nitrophenyl boronic acid (**13**) was attributed a pK_a of 6.9 [58]. Exceptionally, the ortho-substituted nitrobenzeneboronic acid [57] is much less acidic than its para isomer [55] (pK_a 9.2 vs. 7.1, Table 1.2), presumably due to internal coordination of one of the nitro oxygens [52]. One of the most acidic of known boronic acids, with a pK_a of ca. 4.0, is 3-pyridylboronic acid (**14**), which exists mainly as a zwitterion in water (Equation 4, Figure 1.7) [59]. Similarly, benzeneboronic acids of type **15** (Equation 5), which benefit from anchimeric participation of the ortho-dialkylaminomethyl group, display a relatively low pK_a of about 5.2 [61]. In this case, the actual first pK_a is that of ammo-

Table 1.2 Ionization constant (pK_a) for selected boronic acids.

Boronic acid, $RB(OH)_2$	pK_a	Reference
Boric acid, $B(OH)_3$	9.0	53
Methyl	10.4	53
Phenyl	8.9	54
3,5-Dichlorophenyl	7.4	54
3,5-bis(Trifluoromethyl)phenyl	7.2	54
3-Methoxyphenyl	8.7	54
4-Methoxyphenyl	9.3	55
4-Carboxyphenyl	8.4	56
2-Nitrophenyl	9.2	57
4-Nitrophenyl	7.1	55
4-Bromophenyl	8.6	54
4-Fluorophenyl	9.1	54
2-Methylphenyl	9.7	8
3-Methylphenyl	9.0	8
4-Methylphenyl	9.3	8
3,5-Dimethylphenyl	9.1	54
3-Methoxycarbonyl-5-nitrophenyl (**13**)	6.9	58
3-Pyridyl (**14**)	4.0, 8.2	59
8-Quinolinyl	4.0, 10	60
2-($R^1R^2NCH_2$)phenyl (e.g., **15**)	5.2–5.8	61

nium ion deprotonation and formation of the tetrahedral B–N ate adduct **15**. Application of boronic acids of type **15** in the aqueous recognition of saccharides is discussed in Chapter 12.

Boronic acids display Brønsted acidity (cf. Equation 1, Figure 1.6) only in exceptional cases where the formation of a tetrahedral boronate adduct is highly unfavorable. For example, coordination of hydroxide ion to boron in heterocyclic boronic acid derivative **16**, to form **17B**, would break the partial aromatic character of the central ring (Equation 6, Figure 1.7). Indeed, based on ^{11}B NMR and UV spectroscopic evidence, it was suggested that **16** acts as a Brønsted acid in water and forms conjugate base **17A** through direct proton transfer [64]. A few other boronic acids are suspected of behaving as Brønsted acids for the same reasons [65].

1.2.2.4.2 Bimolecular Lewis Acid–Base Complexation under Non-aqueous Conditions

As evidenced by the high pH required in the formation of boronate anions, boronic acids and most dialkyl esters are weak Lewis acids. This behavior contrasts sharply with trialkylboranes, which form strong adducts with phosphines, amines, and other Lewis bases [66]. Aside from the formation of boronate anions, discussed in the previous section, very few stable intermolecular acid–base adducts of boronic acids (esters) exist. Long ago, aliphatic amines and pyridine were found to form complexes in a 1:3 amine:boronic acid stoichiometry [67]. Combustion analyses of these air-stable solids suggested that two molecules of water are lost in the process, which led the authors to propose structure **18** (Equation 7, Figure 1.8). Subsequently, Snyder

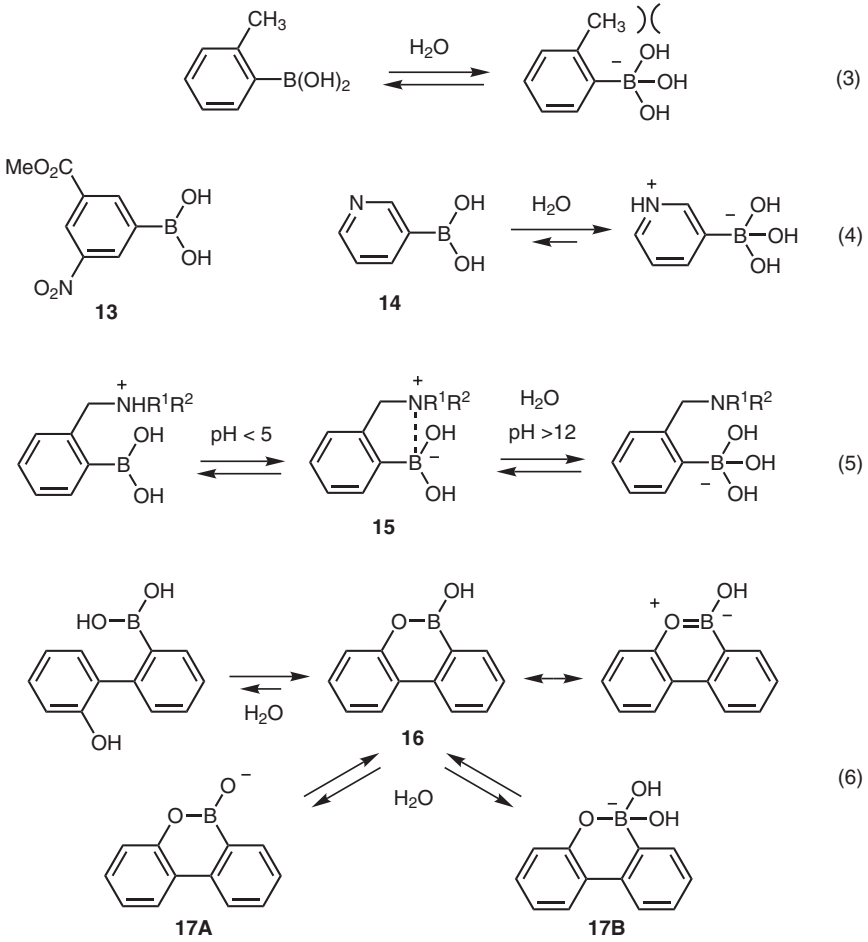
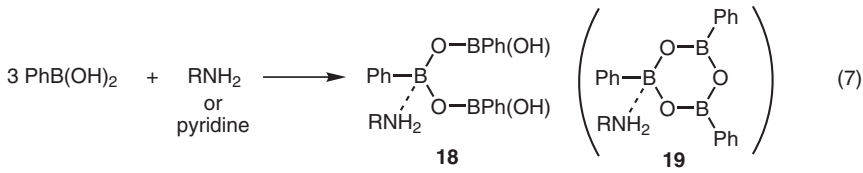
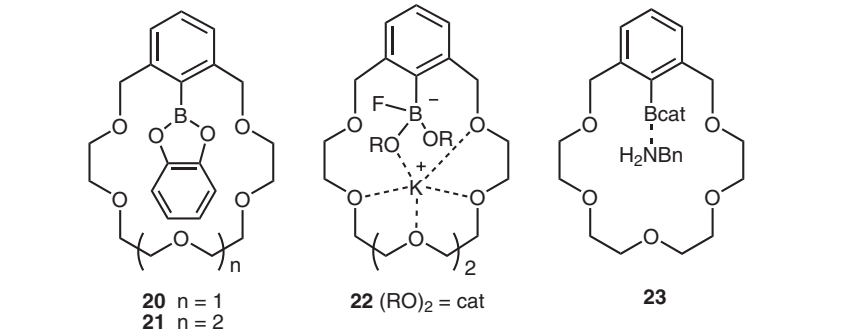


Figure 1.7 Ionization equilibrium for special types of boronic acids.

and co-workers used IR spectroscopy to demonstrate that these 1:3 complexes involved, instead, the fully dehydrated boroxine (**19**) [68]. These complexes are analogous to the diethanolamine boronates discussed in Section 1.2.2.1, although in the latter case the transannular nature of the B–N coordination bond is a highly favorable factor. Catechol boronates are more Lewis acidic and, provided cooperative effects are exploited, bimolecular complexes with fluoride anions and amines have been reported. For example, NMR spectroscopic and X-ray crystallographic studies showed that catechol boronate-containing crown ether **21** forms a stable complex (**22**) with potassium fluoride (Figure 1.8) [69]. The B–F bond strength was thought to be a key factor as other halide salts do not form a similar complex. A synergetic effect from crown ether complexation of potassium also comes into play because the catechol ester of phenylboronic ester did not afford any adduct with KF. Indeed, X-ray structure analysis of complex **22** confirmed this assumption by showing that the potassium





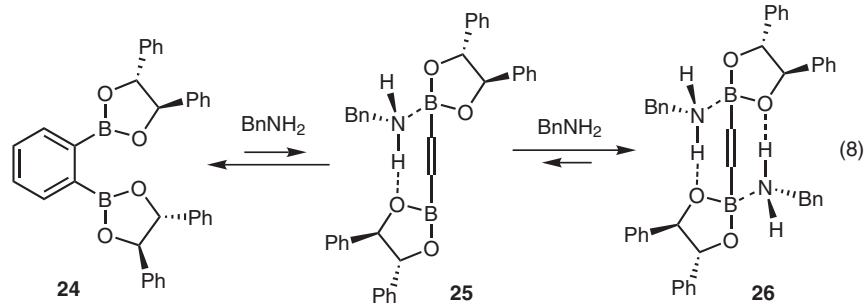


Figure 1.8 Bimolecular Lewis acid–base complexes with boronic esters. cat = catecholato

cation coordinates to five of the six ring oxygens and, interestingly, to one of the boronate oxygens (Figure 1.8). Using the same concept and a similar host, **20**, the primary amine benzylamine bound selectively in a 1:1 fashion to give B–N adduct **23** using the synergy of hydrogen bonds with the ether oxygens [70]. A borylated lyxofuranoside receptor displayed similar behavior [71]. As suggested by ^{1}H NMR spectroscopic studies, an *ortho*-phenyldiboronic ester (**24**) showed cooperative binding of two amine molecules in putative complex **26** (Equation 8, Figure 1.8) [72]. Other diboronate receptors bind to diamines selectively using the two boron centers for B–N coordination [73–75].

1.2.2.5 **Chemical Stability**

1.2.2.5.1 Ligand Exchange and Disproportionation

Several favorable factors contribute to the stability of boronic acids and their esters. Substitution of the carbon-containing group of boronic acids with other substituents is a slow process, and B–C/B–O bond metatheses to give the corresponding disproportionation products (trialkylborane, borinic acid or boric acid) is thermodynamically unfavored [24]. Similarly, thermodynamic considerations make the exchange of the hydroxyl substituents of boronic acids with other ligands quite unfavorable. Substitution with alcohols or diols to form boronic esters usually requires dehydration techniques to drive the reaction forward (Section 1.2.3.2.1). In general, from the B–X bond energies of all possible boronic acid derivatives (RBX_2), free boronic acids remain unchanged when dissolved in solutions containing other potential anionic ligands [24]. The only type of B–X bond stronger than a B–O bond is the B–F bond. Chemical methods to accomplish this type of exchange and other B–O bond derivatizations are described in Sections 1.2.3.6 and 1.2.3.7.

1.2.2.5.2 Atmospheric Oxidation

A significant thermodynamic drive for C–B bond oxidation comes as a direct consequence of the huge difference between B–O and B–C bond energies (Section 1.2.2.1). Heats of reaction for the oxidative cleavage of methylboronic acid with water and hydrogen peroxide are –112 and –345 kJ mol^{-1}, respectively [24]. Yet, fortunately for synthetic chemists, oxidative cleavage of the B–C bond of boronic acid derivatives with water or oxygen is a kinetically slow process, and most boronic acids can be manipulated in air and are stable in water over a wide pH range. This is particularly true for aryl- and alkenylboronic acids, and, in general, samples of all types of boronic acids tend to be significantly more stable when moist (Section 1.2.2.2) [40, 76, 77]. Presumably, coordination of water or hydroxide ions to boron protects boronic acids from the action of oxygen [40, 77]. Exceptionally, the highly electron-poor arylboronic acid 4-carboxy-2-nitrophenylboronic acid (**13**) was reported to undergo slow oxidation to the corresponding phenol when left in aqueous basic solutions (pH 9) [12]. Conversely, basic aqueous solutions of alkylboronate ions were claimed to be highly tolerant of air oxidation [40]. Free alkylboronic acids, however, are quite prone to slow atmospheric oxidation and variable amounts of the corresponding alcohols may form readily when dried samples are left under ambient air with no precautions. Likewise, solutions of arylboronic acids in tetrahydrofuran devoid of stabilizer may turn rapidly into the corresponding phenols. The propensity of alkylboronic acids to undergo autoxidation depends on the degree of substitution, with primary alkyl substituents being less reactive than secondary and tertiary alkyl substituents [76]. More potent oxidants such as peroxides readily oxidize all types of boronic acids and their corresponding esters (Section 1.5.2.1). Hence, this ease of oxidation must be kept in mind when handling boronic acids.

1.2.2.5.3 Protolytic Deboronation

Most types of boronic acids are highly resistant to protolysis of the C–B bond in neutral aqueous solutions, even at high temperatures. For example, *p*-tolylboronic acid was recovered unchanged after 28 hours in boiling water, but it was completely deboronated to toluene after 6 hours under pressure at 130–150 °C [78]. On the other hand, arylboronic acids can be quite readily deboronated in highly acidic or basic aqueous solutions [79]. In particular, ortho-substituted and especially electron-poor arylboronic acids are notorious for their propensity to protodeboronate under basic aqueous conditions – a process that can be exacerbated by exposure to light [59]. Consequently, competitive deboronation may plague some reactions of boronic acids like the Suzuki cross-coupling reaction (Section 1.5.3.1), which is often carried out under basic aqueous conditions. Under strongly acidic aqueous conditions, however, the more electron-rich arylboronic acids deboronate faster [80]. For example, *p*-carboxyphenylboronic acid is more tolerant than phenylboronic acid to the highly acidic conditions of ring nitration under fuming nitric acid and concentrated sulfuric acid [81]. Kuivila and co-workers [81, 82] have studies the effect of acid, temperature, and ring substitution of arylboronic acids on the kinetics of electrophilic protolytic deboronation with strong aqueous acid. A relatively complex behavior was found, and at least two possible pH-dependant mechanisms were proposed. In contrast to their behavior with aqueous acids, most arylboronic acids and esters appear to be very resistant to non-aqueous acids, as evidenced by their recovery from reaction processes using strong organic acids. For example, a phenolic methoxymethyl ether was deprotected with a 2:1 CH_2Cl_2–CF_3CO_2H mixture that left intact a pinacol boronic ester functionality [83]. Exceptionally, one report emphasized that arylboronic acids can be protodeboronated thermally by prolonged heating in refluxing ethereal solvents [84].

In contrast to arylboronic acids, early reports document the great stability of alkylboronic acids under aqueous acidic solutions. For example, various simple alkylboronic acids were unaffected by prolonged heating in 40% aqueous HBr or HI [40]. Like arylboronic acids, however, deboronation is observed in hot basic aqueous solutions [76]. Alkenylboronic esters undergo protonolysis in refluxing AcOH [85], and alkynylboronic acids were reported to be quite unstable in basic aqueous solutions (Section 1.3.5).

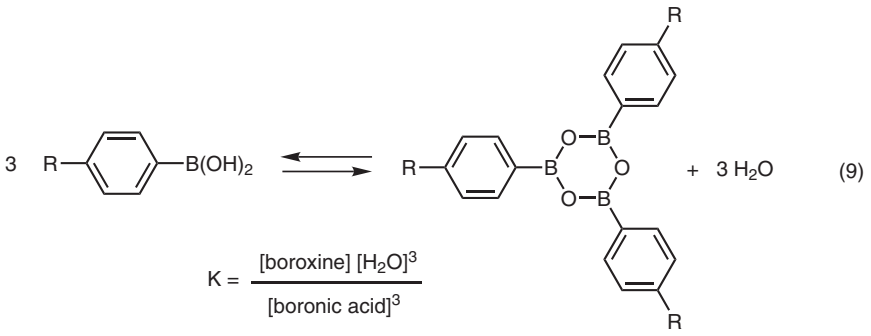
All types of boronic acids can be protodeboronated by means of metal-promoted C–B bond cleavage, and these methods are described separately in Section 1.5.1.

1.2.3
Boronic Acid Derivatives

For convenience in their purification and characterization, boronic acids are often best handled as ester derivatives, in which the two hydroxyl groups are masked. Likewise, transformation of the hydroxyl groups into other substituents such as halides may also provide the increased reactivity necessary for several synthetic applications. The next sections describe the most popular classes of boronic acid derivatives.

1.2.3.1 Boroxines

Boroxines are the cyclotrimeric anhydrides of boronic acids. They are isoelectronic to benzene and, by virtue of the vacant orbital on boron, may possess partial aromatic character. Several theoretical and experimental studies have addressed the nature and structure of these derivatives [86–91]; in particular, X-ray crystallographic analysis of triphenylboroxine confirmed that it is virtually flat [90]. Boroxines are easily produced by the simple dehydration of boronic acids, either thermally through azeotropic removal of water or by exhaustive drying over sulfuric acid or phosphorus pentoxide [40]. These compounds can be employed invariably as substrates in many of the same synthetic transformations known to affect boronic acids, but they are rarely sought as synthetic products. In one rare example of application, the formation of boroxine cross-linkages has been employed to immobilize blue-light emitting oligofluorene diboronic acids [92]. Samples of boroxines may also contain oligomeric acyclic analogues, and they are sensitive to autoxidation when dried exhaustively (Sections 1.2.2.2 and 1.2.2.5.2). A recent study examined the thermodynamic parameters of boroxine formation in water (Equation 9) [93]. Using ^{1}H NMR spectroscopy, the reaction was found to be reversible at room temperature, and the equilibrium constants, relatively small ones, were subject to substituent effects. For example, boroxines with a para electron-withdrawing group have smaller equilibrium constants. This observation was interpreted as an outcome of a back reaction (i.e., boroxine hydrolysis) facilitated by the increased electrophilicity of boron. Steric effects also come into play, as indicated by a smaller *K* for *ortho*-tolylboronic acid than for the para isomer. Variable temperature studies provided useful thermodynamic information, which was consistent with a significant entropic drive for boroxine formation due to the release of three molecules of water.



1.2.3.2 Boronic Esters

By analogy with carboxylic acids, replacement of the hydroxyl groups of boronic acids by alkoxy or aryloxy groups provides esters. By losing the hydrogen bond donor capability of the hydroxyl groups, boronic esters are less polar and easier to handle. They also serve as protecting groups to mitigate the particular reactivity of boron–carbon bonds. Most boronic esters with a low molecular weight are liquid at room temperature and can be conveniently purified by distillation. Exceptionally, the trity-

loxymethyl esters described above (**7**, Figure 1.2) are crystalline solids [17]. Figure 1.9 shows a selection of the most commonly encountered boronic esters, many of which are chiral and have also been used as inducers in stereoselective reactions (Chapters 6 and 8). Several macrocyclic oligomeric esters have also been described [94].

1.2.3.2.1 Stoichiometric Formation

The synthesis of boronic esters from boronic acids and alcohols or diols is straightforward (Equation 10, Figure 1.9). The overall process is an equilibrium, and the forward reaction is favored when the boronate product is insoluble in the reaction solvent. Otherwise, ester formation can be driven by azeotropic distillation of the water produced using a Dean-Stark apparatus, or, alternatively, with the use of a dehydrating agent (e.g., $MgSO_4$, molecular sieves). Boronic esters can also be made by transesterification of smaller dialkyl esters like the diisopropyl boronates, with distillation of the volatile alcohol by-product driving the exchange process. For cyclic esters made from the more air-sensitive alkylboronic acids, an alternate method involves treatment of a diol with lithium trialkylborohydrides [95]. Likewise, cyclic ethylboronates have been prepared by reaction of polyols with triethylborane at elevated temperatures [96]. One of the first reports on the formation of boronic esters from diols and

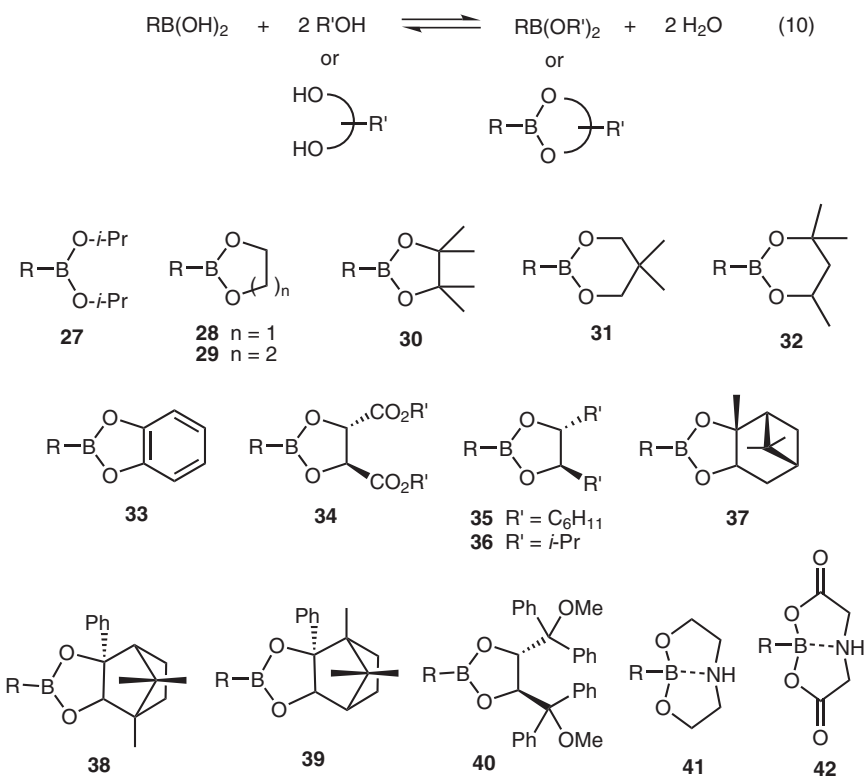


Figure 1.9 Common boronic esters.

polyols, by Kuivila and co-workers, described the preparation of several esters of phenylboronic acid by reaction of the latter, in warm water, with sugars like mannitol and sorbitol, and 1,2-diols like catechol and pinacol [97]. The desired non-polar boronic esters precipitated upon cooling the solution. Interestingly, *cis*-1,2-cyclohexanediol failed to provide the corresponding cyclic ester and the authors rationalized this observation on the basis of the unfavorable geometry of the diol substrate. Thus, whereas the two diols are not oriented in the same plane in the chair conformation (Equation 11, Figure 1.10), they can adopt such a favorable orientation only in the boat conformer, which is thermodynamically unfavorable [97].

Under anhydrous conditions (i.e., refluxing acetone), phenylboronic esters of *cis*-1,2-cyclopentanediol and *cis*-1,2-cyclohexanediol can be isolated [98]. The trans isomers, however, still fail to give a 1:1 adduct, and, based on elemental analysis and molecular weight determinations, give, rather, 1:2 adducts such as **43** (Equation 12). This observation was also explained in terms of the large energy required for the trans-diol to adopt a coplanar orientation, which would increase ring strain and steric interactions between axial atoms. Recently, the marked preference for the formation of boronic esters with cis-diols was exploited in the concept of dynamic combinatorial chemistry. In this study, phenylboronic acid was used as a selector to amplify and accumulate one out of nine possible dibenzoate isomers of *chiro*-inositol that exist under equilibrating conditions through base-promoted intramolecular acyl migration (Equation 13) [99]. Diethanolamine boronic esters (**41**, Figure 1.9) represent a useful class of boronic acid derivatives [100]. Other N-substituted derivatives were also characterized [101]. The internal coordination between the nitrogen lone pair and boron's

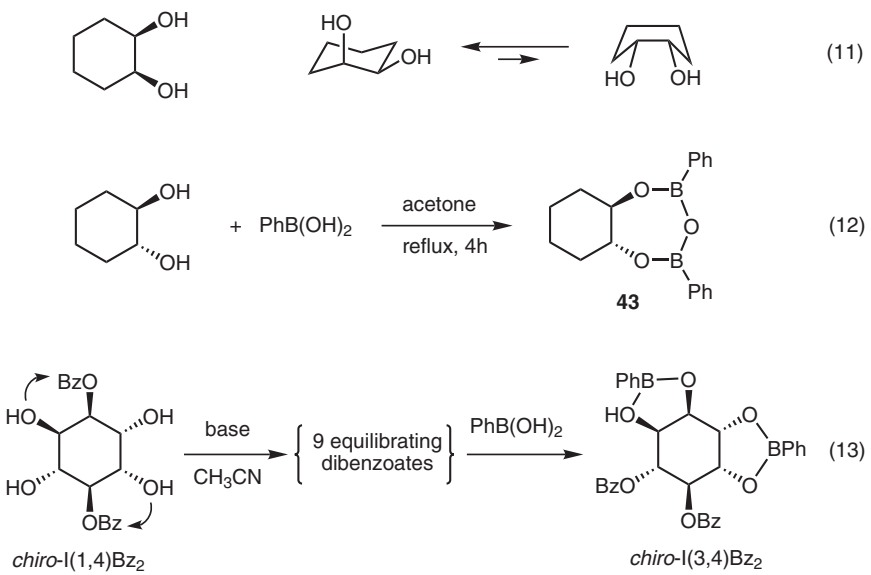


Figure 1.10 Specific examples of boronic ester formation with cyclic diols.

vacant orbital constitutes a rather unique structural characteristic of these tetrahedral derivatives. This coordination makes the hydrolysis reaction less favorable, and even stabilizes the boron atom against atmospheric oxidation. Analogous iminodiacetic acid derivatives (**42**) are even more robust (B–N $\Delta G^{\neq} > 90$ vs. 60 kJ mol^{-1} for **41**) [21]. Compared to the alkoxy groups of **41**, the electronic effect of the carboxyl groups leads to a more acidic boron atom, and hence a stronger B–N interaction. Diethanolamine boronic esters can be conveniently formed in high yields, often without any need for dehydration techniques, as they tend to crystallize out of solution. Indeed, diethanolamine adducts are solids, often crystalline, with sharp melting points, and can thus be used for purifying and characterizing boronic acids. The concept of internal coordination in diethanolamine esters has been exploited in the development of the DEAM-PS resin for immobilization and derivatization of boronic acids (Section 1.4.2.1).

1.2.3.2.2 Hydrolysis and Cleavage

Thermodynamically, the stability of B–O bonds in boronic acids and their ester derivatives is comparable (Section 1.2.2.1). Consequently, hydrolysis, in bulk water or even by simple exposure to atmospheric moisture, is a threatening process while handling boronic esters that are kinetically vulnerable to attack of water. In fact, hydrolysis is very rapid for all acyclic boronic esters such as **27** (Figure 1.9), and for small unhindered cyclic ones like those made from ethylene or propylene glycol (**28** and **29**), and tartrate derivatives (**34**) [102]. Catechol esters (**33**) are another class of popular derivatives as they are the direct products of hydroboration reactions with catecholborane (Section 1.3.4.4). Due to the opposing conjugation between the phenolic oxygens and the benzene ring, these derivatives are more Lewis acidic and are quite sensitive to hydrolysis. In the hydrolytic cleavage of catechol boronic esters from hydroborations, it is often necessary to carefully monitor the pH and buffer the acidity of the released catechol.

Conversely, hydrolysis can be slowed considerably for hindered cyclic aliphatic esters such as the C2-symmetrical derivatives **35** [103] and **36** [104], pinacol (**30**) [97], pinanediol (**37**) [105], Hoffmann's camphor-derived diols (**38** and **39**) [106], and the newer one **40** [107]. Indeed, many of these boronic esters tend to be stable to aqueous workups and silica gel chromatography. The robustness of the esters of *trans*-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol (**40**) was demonstrated in its applications as a protecting group for alkenylboronic acids [107]. The resulting alkenylboronic esters are tolerant to a wide variety of reaction conditions (Section 1.3.8.5). Unfortunately, the bulky boronic esters **37**–**40** are very robust to hydrolysis, and their conversion back into boronic acids is notoriously difficult. Removal of the bulky pinanedioxy group in **37** exemplifies the magnitude of this particular problem. It is generally not possible to cleave a pinanediol ester quantitatively in water even under extreme pH conditions. Cleavage can be achieved by transborylation with boron trichloride [23, 108–112], which destroys the pinanediol unit, or by reduction to the corresponding borane using lithium aluminum hydride [113] (Equations 14 and 15, Figure 1.11). Both derivatives can be subsequently hydrolyzed to afford the desired boronic acid. Recently, a mild approach was developed to convert the robust DICHED

and pinanediol esters into trifluoroborate salts [114]. A two-phase transesterification procedure with phenylboronic acid has been described, but it is applicable only to small, water-soluble boronic acids [115]. Many of these procedures, such as the BCl_3-promoted method, were applied to the particular case of pinanediol esters of α-acylaminoalkylboronic acids [23, 112]. Using such a substrate, **44**, an oxidative method allowed the recovery of free boronic acid **45** in good yield from a destructive periodate cleavage, or by using the biphasic transesterification method in hexanes–water (pH 3) (Equations 16 and 17, respectively, Figure 1.11) [116].

Hydrolysis of a series of 5-, 6-, and 7-membered phenylboronic esters was studied by measuring the weight increase of samples subjected to air saturated with water vapor (i.e., under neutral conditions) [117]. Hydrolysis was confirmed by the observation of phenylboronic acid deposits. This early study confirmed that hindered esters such as phenylboron pinacolate hydrolyze at a much slower rate, and that 6-membered boronates are more resistant to hydrolysis than the corresponding 5-membered analogues. These results were interpreted in terms of the relative facility of boron–water complexation to form a tetracoordinate intermediate. Two factors were proposed: (1) the increase of steric effects on neighboring atoms upon formation of the hydrated complex and (2) the release of angle strain, which is optimal in the 5-membered boronates due to the decrease of the O–B–O and B–O–C bond angles

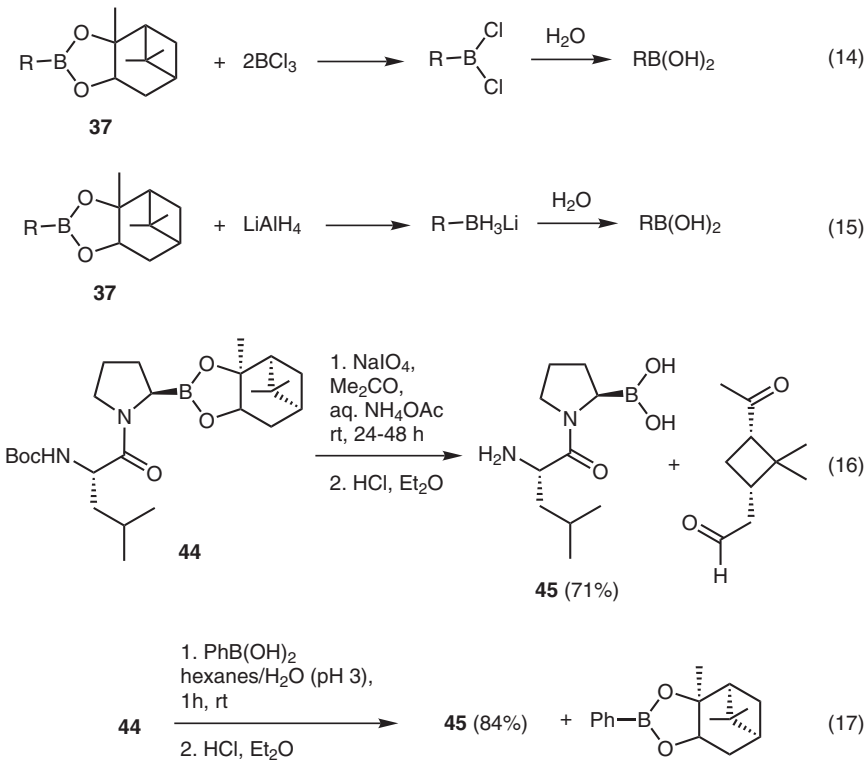
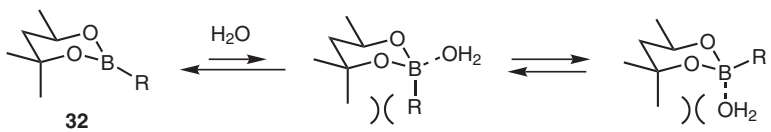


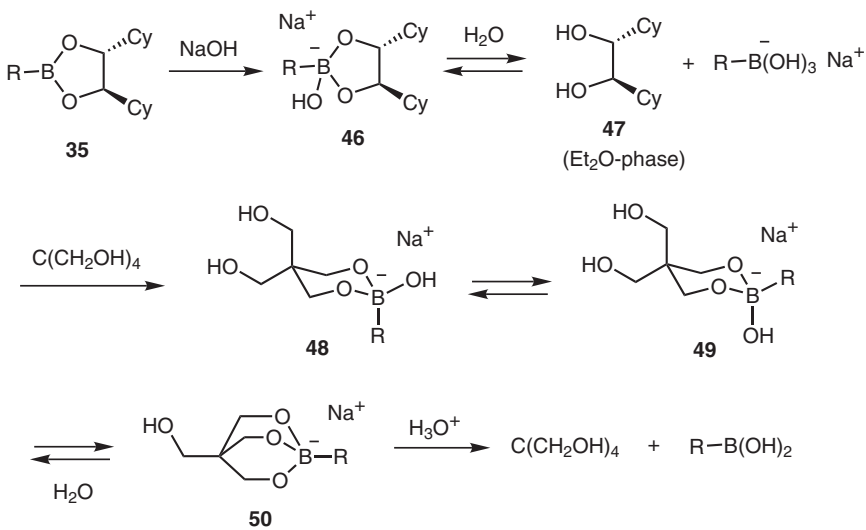
Figure 1.11 Cleavage of pinanediol boronic esters.

from ca. 120° to 109° upon going from a planar configuration to the tetracoordinate hydrated form with tetrahedral B and O atoms. Propanediol derivative **32** emphasizes the importance of steric hindrance to the coordination of water in order to minimize kinetic hydrolysis. Hydrolysis of **32** is slowed considerably compared to the unsubstituted 1,3-propanediol ester (**29**). The superior stability of esters **32** towards hydrolysis was attributed to the axial methyl groups, which develop a 1,3-diaxial interaction with the boron center in the approach of water from either face (Equation 18). Likewise, in contrast to the corresponding dimethyl ester, it was shown that atmospheric polymerization of 2-vinyl-4,4,6-trimethyl-1,3,2-dioxaborinane was largely prevented, presumably due to the hindered approach of oxygen to boron [118].



32 (18)

While developing a novel two-phase system for the basic hydrolysis of DICHED esters, **35**, Matteson has put forward a useful generalization on the process of thermodynamic hydrolysis of boronic esters (Scheme 1.1) [119]. Using a relatively dilute nonmiscible mixture of 1M aqueous sodium hydroxide and diethyl ether (conditions required to avoid precipitation of boronate salt **46**), an equilibrium ratio of 42:1 (**47** to **35**) in the ether phase was reached only after 18 hours even by using a large excess of sodium hydroxide with respect to the boronic ester **35**. By making use of soluble triols such as pentaerythritol to transesterify salt **46** into a more water-soluble salt (i.e., **48**/**49**/**50**), and thus facilitating the liberation of DICHED, a higher ratio of 242:1 was



Scheme 1.1 Hydrolysis of boronic esters by a two-phase system.

obtained. The free boronic acid could then be recovered by acidification of the aqueous phase containing a mixture of **48**–**50**, followed by extraction with ethyl acetate.

This new procedure, however, was not successful for the complete hydrolysis of pinanediol phenylboronic ester, providing an optimal pinanediol:boronic ester ratio of 3.5:1 in the ether phase. These results were interpreted in terms of the determining thermodynamic factors that control the reversible hydrolysis or transesterification of boronic esters. Entropic factors in the hydrolysis of cyclic esters are unfavorable as three molecules are converted into only two. In this view, transesterification with a diol, instead of hydrolysis, is overall even and thus more favorable. Other factors affecting the equilibrium are the effect of steric repulsions on enthalpy as well as the entropies of internal rotation of the free diols. trans-4,5-Disubstituted dioxaborolanes such as DICHED esters present minimal steric repulsions as the two cyclohexyl substituents eclipse C–H bonds. On the contrary, pinacol esters experience significant steric repulsion from the four eclipsing methyl groups. Consequently, it is not surprising that they can be transesterified easily with trans-DICHED [17, 120]. In this scenario, the exceptional resistance of pinanediol esters to thermodynamic hydrolysis would be due to the rigid cyclic arrangement whereby the two diols are preorganized in a coplanar fashion to form a boronic ester with essentially no loss of entropy from internal rotation of the free pinanediol. Other types of esters including DICHED [121] and the robust pinacol esters of peptidyl boronates [122] have also been converted into boronic acids through transesterification with diethanolamine in organic solvent, followed by acidic aqueous hydrolysis. This method, however, is effective only if the resulting diethanolamine ester crystallizes from the solution so as to drive the equilibrium forward. As stated above, transesterification of cyclic boronic esters with diols is often slow, and particularly so in organic solvents. Wulff and coworkers found that several boronic acids possessing proximal basic atoms or substituents (e.g. **15**, Figure 1.7) lead to an unusually large neighboring group effect, and the transesterification equilibria is reached much faster with these boronic esters as a result of a rapid proton transfer [123]. Boronic acids like **15** are internally coordinated (^{11}B NMR = 14.6 ppm), and beneficial neighboring effects in these *ortho*-aminomethylbenzeneboronic acids are at play in the aqueous binding of carbohydrates (Chapter 12).

1.2.3.2.3 Boronic Acid–Diol (Sugar) Equilibrium in Water

The reversible formation of boronic esters by the interaction of boronic acids and polyols in water was first examined in the seminal study of Lorand and Edwards [49]. This work followed an equally important study on the elucidation of the structure of the borate ion [124]. By measuring the complexation equilibrium between phenylboronic acid and several model diols and monosaccharides using the method of pH depression, ester formation was shown to be more favorable in solutions of high pH where the boronate ion exists in high concentrations (Equation 19, Figure 1.12). This study also confirmed the Lewis acid behavior of boronic acids and the tetracoordinate structure of their conjugate base, i.e., the hydroxyboronate anion (Section 1.2.2.4). Another conclusion is that free boronic acids have lower Lewis acid strengths than their neutral complexes with 1,2-diols. For example, the pK_a of $PhB(OH)_2$ decreases

from 8.8 to 6.8 and 4.5 upon formation of cyclic esters with glucose and fructose, respectively [125]. To explain the favorable thermodynamic effect seen at high pH (Equation 19) in comparison to neutral pH (Equation 20), it was hypothesized that the formation of hydroxyboronate complexes of 1,2-diols is accompanied by a significant release of angle strain, resulting from the rehybridization of boron from sp^2 to sp^3 (i.e., 120° vs. 109° bond angles) [49].

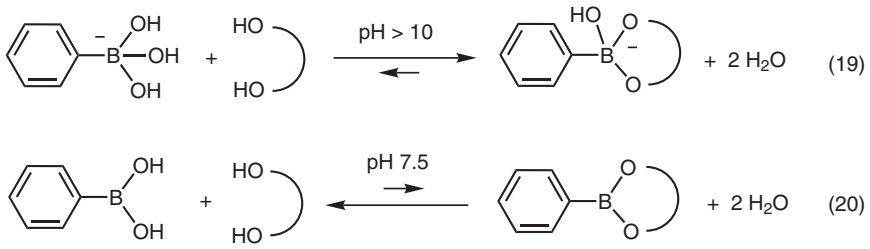


Figure 1.12 Equilibrium formation of boronic esters from diols at high (Equation 19) and neutral (Equation 20) pH in water.

Pizer and co-workers reported a series of investigations on the equilibria and mechanism of complexation between boric acid or boronic acids with polyols and other ligands in water. Early work by this group [53] and others [126] showed that the stability constants of complexes increase when the aryl substituent on the boronic acid is electron poor, which is consistent with the proposal of Lorand and Edwards that views formation of hydroxyboronate complexes as the drive for release of angle strain. Using methylboronic acid and simple 1,2- and 1,3-diols, equilibrium constants were measured both by pH titration and ^{11}B NMR spectroscopy [127]. Constants of 2.5, 5.5 and 38 were found for 1,3-propanediol, 1,2-ethanediol and 1,2,3-propanetriol respectively, with the latter binding preferentially with a 1,2-diol unit. Kinetic studies performed by the temperature-jump relaxation method revealed forward and reverse rate constants, and established that the lower stability constants of six-membered boronic esters compared to the five-membered ones is the result of a faster reverse reaction for the former [127]. Quite importantly, this work confirmed that the tetracoordinate hydroxyboronate anion is much more reactive than the trigonal neutral boronic acid in forming esters with diols (at least 10^4 times faster), with forward rate constants in the range 10^3–10^4 M^{-1} s^{-1}. It was suggested that the high reactivity of the boronate anion could be interpreted in terms of an associative transition state involving proton transfer and hydroxide displacement within a pentacoordinated boron. In the past decade, interest in the interaction between boronic acids and cis-diols has developed tremendously due to applications in the development of receptors and sensors for saccharides (Section 1.6.4 and Chapter 12). As with simple polyols discussed above, the binding of carbohydrates to boronic acids is subject to the same geometrical requirement for a coplanar diol unit. In fact, in water, boronic acid receptors bind to glucose in the furanose form, which presents a very favorable, coplanar 1,2-diol [128]. This observation concurs with the absence of complexation between boronic acids and non-reducing sugars (glycosides) and the low affinity of

1→4 linked oligosaccharides such as lactose [129, 130]. Fluorescent catechol derivatives such as the dye alizarin red S (ARS) also form covalent adducts with boronic acids in water, and this equilibrium has recently been used as a competitive color- and fluorescence-based assay for both qualitative and quantitative determination of saccharide binding [131]. Using the ingenious ARS assay, Springsteen and Wang presented an interesting cautionary tale from discrepancies found in the measurements of boronic acid–diol binding constants based on the above-mentioned method of pH depression. The latter method may not always reliably provide the true overall equilibrium constants. Indeed, these measurements are complicated by the multiple states of ionization of the boronic acid and the resulting ester (neutral trigonal or tetrahedral hydroxyboronate), the pronounced effect of the solvent, pH and buffer components, and the concentration of these species on the equilibrium [125].

1.2.3.3 Dialkoxyboranes and other Heterocyclic Boranes

Several cyclic dialkoxyboranes, such as 4,4,6-trimethyl-1,3,2-dioxaborinane **51** [132], 1,3,2-benzodioxaborole (catecholborane) **52** [133], pinacolborane **53** [134], have been described (Figure 1.13). Dialkoxyboranes can be synthesized simply by the reaction between equimolar amounts of borane and the corresponding diols. These borohydride reagents have been employed as hydroborating agents, in carbonyl reduction, and more recently as boronyl donors in cross-coupling reactions. Dialkoxyboranes have also been invoked as intermediates in the hydroboration of β,γ-unsaturated esters [135]. Sulfur-based heterocyclic boranes were reported, including 1,3,2-dithiaborolane **54** [136]. Acyloxyboranes such as Yamamoto's tartaric acid derived CAB catalyst (**55**) [137] and related oxazaborolidinones such as **56**, derived from N-sulfonylated amino acids, have been used as chiral promoters for cycloadditions and aldol reactions of silyl enol ethers [138]. Synthetic applications of these catalysts are described in detail in Chapter 10.

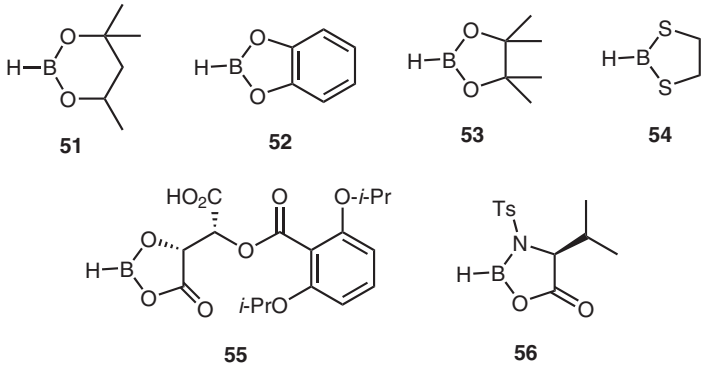
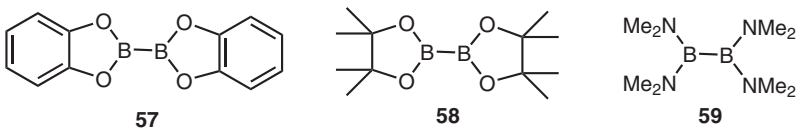


Figure 1.13 Common dialkoxyboranes and heterocyclic analogues.

1.2.3.4 Diboronyl Esters

Various synthetically useful diboronyl esters such as B_2cat_2 (**57**) or B_2pin_2 (**58**) have been described (Figure 1.14) [139]. These reagents are now commercially available, albeit their cost remains quite prohibitive for preparative applications. They can be accessed by condensation of a diol with the tetrakis(dimethylamino)diboron precursor (**59**), which is also commercially available and can be made in three steps from boron tribromide [140]. Recently, a shorter and more practical synthesis of B_2cat_2 was described [141]. The discovery that diboronyl compounds can be employed with transition metal catalysts in various efficient cross-coupling and addition reactions can be considered one of the most significant advances in boronic acid chemistry in the past decade. The chemistry of diboronyl compounds has been reviewed recently [139], and is discussed in several sections of this chapter and in Chapter 2.



57 **58** **59**

Figure 1.14 Common diboronyl reagents.

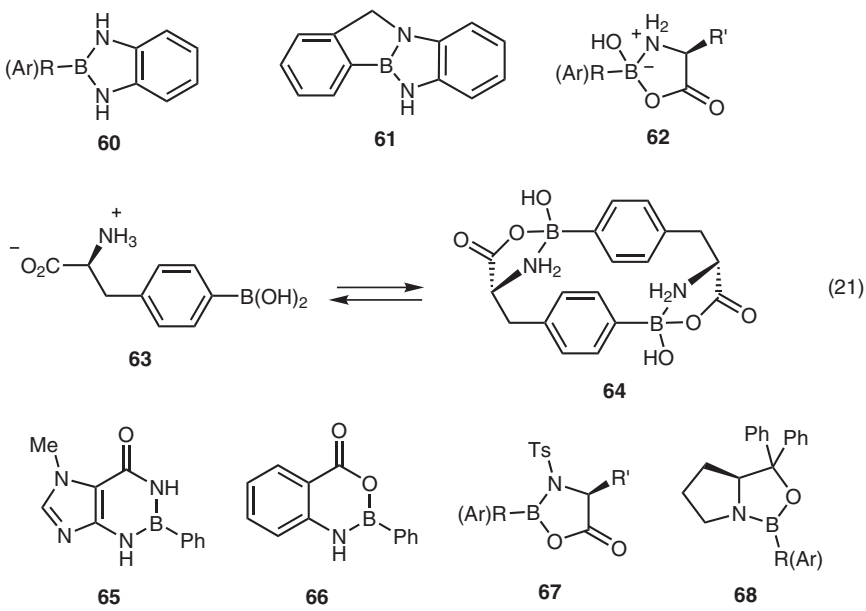
1.2.3.5 Azaborolidines and other Boron Heterocycles

Numerous heterocyclic derivatives of boronic acids have been described, and useful X-ray crystallographic data have been obtained for many of these compounds. Some representative examples are described in this section (Figure 1.15). Benzodiazaborole products (**60**) of 1,2-phenylenediamine and free boronic acids form readily in refluxing toluene [142, 143]. Both aliphatic and aromatic acids are applicable, and it was claimed that the resulting adducts are easier to recrystallize than diethanolamine boronates. An intramolecular adduct, **61**, was also reported [144]. These benzodiazaboroles are air-stable, and the adduct of phenylboronic acid hydrolyzes only slowly in aqueous solutions. With anhydrous hydrogen chloride in toluene, a dihydrochloride salt was formed. The unusual stability of adducts **60** was further supported by their formation by exchange of tartrate esters with 1,2-phenylenediamine at room temperature in benzene. Control studies showed that the equilibrium lies much towards the diazaborole, which is surprising in light of thermodynamic factors such as the much higher energy of covalent B–O bonds than B–N bonds (Section 1.2.2.1). As both ethylenediamine and aniline itself did not form similar covalent adducts under the same conditions, it was suggested that the favorable geometry of 1,2-phenylenediamine, as well as the stability of the resulting five-membered ring and its partial aromatic character, were responsible for the highly favorable formation of adducts **60** [142]. Diazaborolidines from aliphatic 1,2-diamines, however, are not prepared with such ease. For example, several chiral ones evaluated as chiral proton sources had to be prepared from dichloroboranes [145].

Amino acids can condense with boronic acids to form 1:1 chelates of type **62** [146]. The tetracoordinate structure of these adducts is very apparent by NMR due to the formation of a new stereocenter at boron. Interestingly, 4-boronophenylalanine (**63**),

a potential BNCT agent, was shown to dimerize to form head-to-tail paracyclophane derivative **64** in reversible fashion in DMSO (Equation 21, Figure 1.15) [147]. This dimer is prevalent at low concentrations (<50 mM), while oligomeric mixtures predominate at higher concentrations. Amino acid adducts of boronic acids are hydrolytically unstable, and **64** was indeed found to revert to free **63** upon addition of water to the solution. Purine analogue **65** also hydrolyzed readily in aqueous ethanolic solutions [148]. The addition product **66** between anthranilic acid and phenylboronic acid has been reported [149]. Salicylhydroxamic acid adducts of arylboronic acids are more resistant and were proposed as components of an affinity system for bioconjugation [150] (Section 1.6.8). Both B-alkyl and B-aryl oxazaborolidinones **67**, made from N-sulfonylated amino acids such as tryptophan, have been employed as chiral Lewis acids in several synthetic transformations (Chapter 10) [151], and in crystallization-induced asymmetric transformations [152]. Aminoalcohols can form oxazaborolidines by condensation with boronic acids under anhydrous conditions. Chiral oxazaborolidines derived from reduced amino acids (e.g., **68**) have been a popular class of Lewis acids for cycloadditions (Chapter 10) [153], and as catalysts and reagents for the enantioselective reduction of ketones and imine derivatives [154], which is described in detail in Chapter 11.

In addition to the benzoboroxole described in Section 1.2.2.1 (**8**, Figure 1.2) [18, 155, 156], there are several other examples of "internal" heterocyclic derivatives in which an ortho substituent of an arylboronic acid closes onto the boronic acid with either a dative or a covalent bond [157]. For example, *ortho*-anilide derivatives **69** and the corresponding ureas (**70**), in a putative internally chelated form A, were shown to



(21)

Figure 1.15 Examples of azaborolidines and other heterocyclic analogues.

exist mainly in their cyclic monodehydrated form B (Equation 22, Figure 1.16) [158]. This is probably true even in aqueous or alcohol solutions owing to the partial aromatic character of these boron-containing analogues of purine heterocycles. In fact, these compounds can even add one molecule of water or alcohol by 1,4-addition and thus exist in equilibrium with form C. One such derivative, **71**, was obtained from recrystallization in methanol, and X-ray crystallographic analysis proved its zwitterionic structure with a tetrahedral boronate anion. A class of related derivatives made from 2-formylphenylboronic acid and hydrazines was also characterized [157], and the boroxine of one internally chelated derivative, **72**, was studied by X-ray crystallography [159]. Other examples of heterocyclic derivatives include pyrimidine analogue **73** and cyclodimer **74** [160].

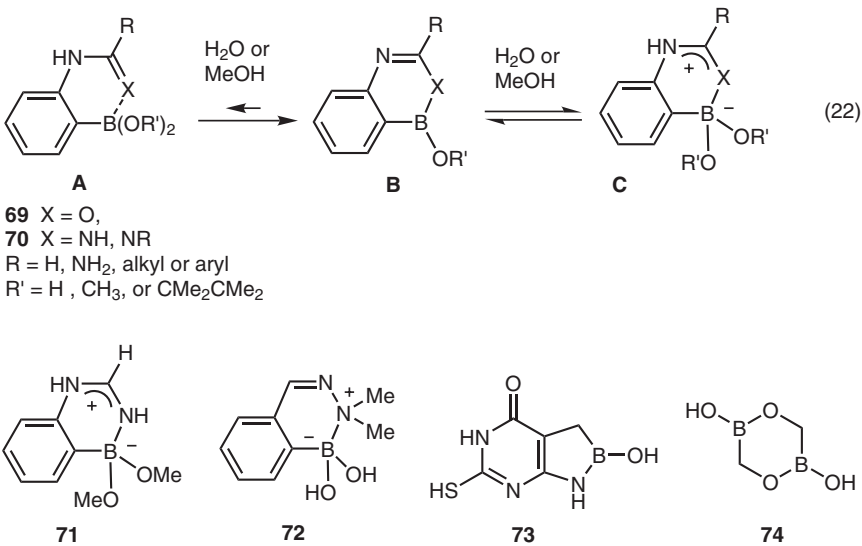


Figure 1.16 Hemi-heterocyclic "internal" boronic ester derivatives.

1.2.3.6 **Dihaloboranes and Monoalkylboranes**

Highly electrophilic dihaloboranes can undergo reactions that do not affect boronic acids and esters. For example, oxidative amination of the B–C bond of boronate derivatives requires the transformation of boronic esters into the corresponding dichlorides (Section 1.5.2.2). Of several methods described for the preparation of alkyl- and aryl-dichloroboranes, only a few conveniently employ boronic acids and esters as substrates. They can be accessed either by iron trichloride-catalyzed exchange of the boronic ester with BCl_3 (Equation 23, Figure 1.17) [161] or by treatment of the corresponding monoalkylborane with TMSCl [162] or acidification with anhydrous HCl in dimethyl sulfide (Equation 24) [163]. The requisite monoalkyl and monoaryl borohydride salts can be made by treating boronic esters with $LiAlH_4$ [164], and the use of HCl in dimethyl sulfide leads to the isolation of the stable $RBCl_2$-SMe_2 adducts (Equation 24) [163]. Both methods can be performed without detectable epimerization on

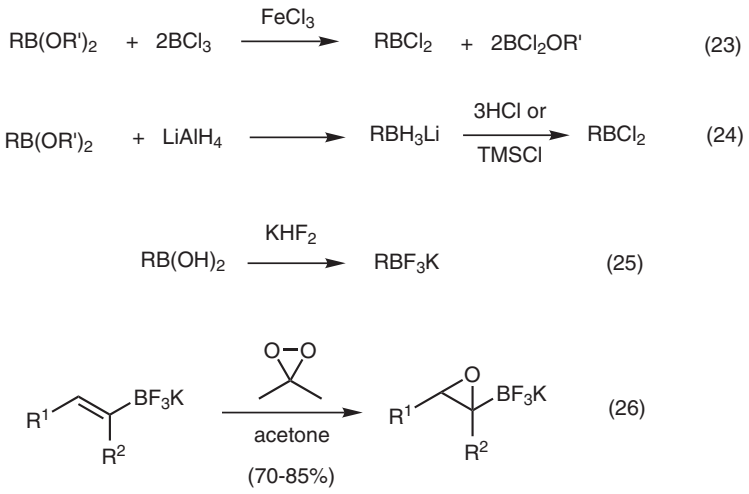


Figure 1.17 Synthesis of dichloroboranes, monoalkylboranes, and trifluoroborate salts.

chiral boronic esters originating from the asymmetric hydroboration of alkenes [161, 163].

1.2.3.7 **Trifluoroborate Salts**

Organotrifluoroborate salts are a new class of air-stable boronic acid derivatives that can be easily prepared according to a procedure described by Vedejs and co-workers (Equation 25, Figure 1.17) [165]. Boronic esters also react to give the desired salts [114]. These crystalline derivatives are easy to handle, and are competent substrates in many of the same reaction processes that employ free boronic acids. Their applications have been reviewed recently [166]. Notable examples include the Suzuki cross-coupling reaction [167], rhodium-catalyzed 1,4-addition [168], copper-promoted couplings to amines and alcohols [169], and allylation of aldehydes [170]. It was recently reported that trifluoroborate salts are conveniently transformed into dichlororoboranes by treatment with $SiCl_4$ in THF [171]. The incompatibility of boron–carbon bonds with several oxidants limits the possibilities to further transform compounds containing a boronic acid (ester) functionality. Taking advantage of strong B–F bonds, the use of organotrifluoroborate salts may be viewed as a way to protect boron's vacant orbital from an electrophilic reaction with a strong oxidant. Molander and Ribagorda have recently provided a clear testimony of this significant advantage provided by trifluoroborate salts. In this protocol, 1-alkenyltrifluoroborate salts were epoxidized cleanly with preservation of the carbon–boron bonds in good yields and high purity with dimethyldioxirane (Equation 26, Figure 1.17) [172]. The latter was clearly superior to *m*-CPBA and other oxidants tested. Significantly, under the same conditions, 1-alkenylboronic acids and the corresponding pinacol esters do not lead to the desired epoxide. Instead, the aldehyde resulting from carbon–boron oxidation and

other unidentified oxidation products are obtained. In view of their unique properties, interest in the chemistry of trifluoroborate salts is expected to grow further.

1.3 Synthesis of Boronic Acids and their Esters

The increasing importance of boronic acids as synthetic intermediates has justified the development of new, mild and efficient methods to provide access to a large pool. Of particular interest is the synthesis of arylboronic acids substituted with a wide range of other functional groups. As a consequence of their growing popularity and improvements in methods available for their preparation, many functionalized boronic acids have become available from several commercial sources. Although several methods, like the oxidation or hydrolysis of trialkylboranes, have significant historical and fundamental relevance, this section is devoted mainly to modern methods of practical value to synthetic chemists.

1.3.1 Arylboronic Acids

Arylboronic acids remain the most popular class of boronic acids. Their popularity in medicinal chemistry is due in large part to their role as cross-coupling partners for the synthesis of biaryl units (Section 1.5.3.1), which are present in the structure of several pharmaceutical drugs. Several methods, summarized generically in Figure 1.18, are now available for the synthesis of complex arylboronic acids and the following section presents an overview of these methods with selected examples in Table 1.3.

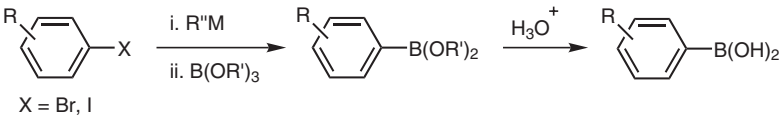
1.3.1.1 Electrophilic Trapping of Arylmetal Intermediates with Borates

One of the first and, probably, still the cheapest and most common way of synthesizing arylboronic acids involves the reaction of a hard organometallic intermediate (i.e., lithium or magnesium) with a borate ester at low temperature. The corresponding zinc and cadmium species are much less effective [173].

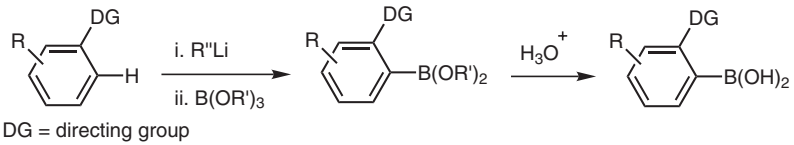
1.3.1.1.1 By Metal–Halogen Exchange with Aryl Halides

Provided the aryl halide substrate is compatible with its transformation into a strongly basic and nucleophilic arylmetal reagent, relatively simple aryl, alkenyl and even alkylboronic acids can be made from a sequence of metal–halogen exchange followed by electrophilic trapping with a trialkylborate. The first such methods for preparing phenylboronic acid, which involved the addition of methylborate to an ethereal solution of phenylmagnesium bromide at –15 °C, became notorious for providing a low yield of desired product [174]. Boron trifluoride was also employed instead of borates [175]. In the early 1930s, Johnson and co-workers developed the first practical and popular method for preparing phenylboronic acid and other arylboronic acids with an inverse addition procedure meant to minimize the undesirable formation of

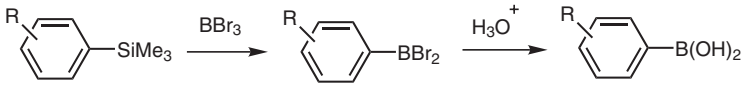
1.3.1.1.1 Electrophilic borate trapping of arylmetal intermediates from aryl halides



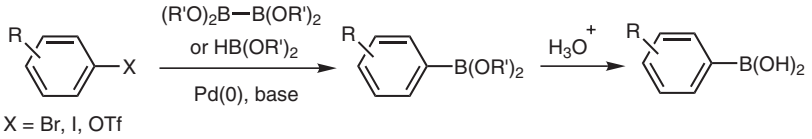
1.3.1.1.2 Electrophilic borate trapping of arylmetal intermediates from directed ortho-metallation



1.3.1.2 Transmetallation of arylsilanes and arylstannanes



1.3.1.3 Transition metal-catalyzed coupling between aryl halides/triflates and diboronyl reagents



1.3.1.4 Direct boronylation by transition metal-catalyzed aromatic C-H functionalization

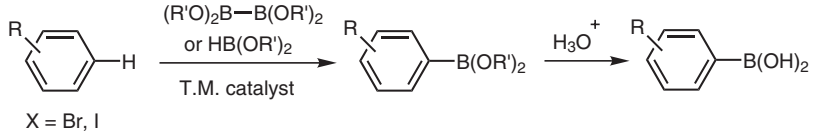


Figure 1.18 Common methods for the synthesis of arylboronic acids (esters).

borinic acid by-product [176, 177]. In this variant, phenylmagnesium bromide is added to a solution of tri-*n*-butylborate at –70 °C. Specifically, in the reaction of an arylmagnesium bromide with a trialkylborate, exhaustive formation of undesired borinic acid and borane via a second and third displacement on the intermediate boronate ester is prevented by precipitation of the magnesium trialkoxyphenylborate salt (**75**, M = MgX, in Equation 27, Figure 1.19). The latter is also thought not to dissociate into the corresponding boronic ester and metal alkoxide at low temperatures, which is key in protecting the desired boronate ester from a second displacement by the Grignard reagent (Equation 28). Then, the free boronic acid is obtained following a standard aqueous workup to hydrolyze the labile boronic ester substituents. Such procedures have been used successfully in the kilogram-scale preparation of important arylboronic acids [178, 179].

Table 1.3 Selected examples of preparative methods for arylboronic acids and esters. pin = pinacolato ($OCMe_2CMe_2O$).

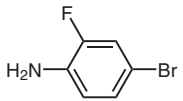
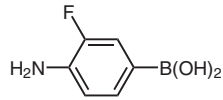
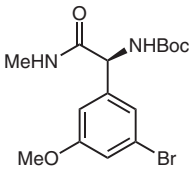
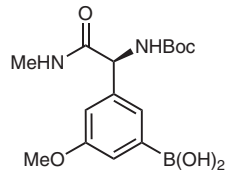
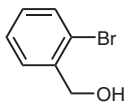
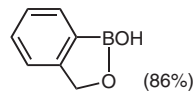
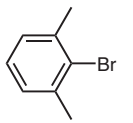
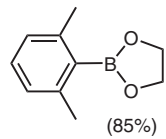
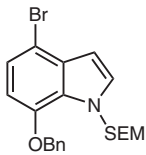
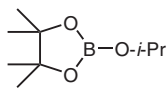
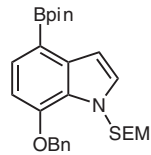
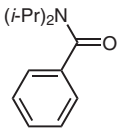
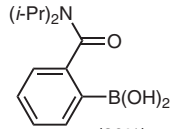
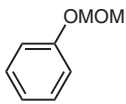
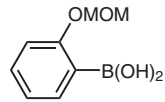
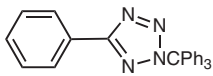
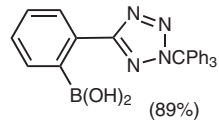
Entry	Substrate	Conditions	Product	Reference
1		1. i. *n*-BuLi (2 eq), THF, 0 °C ii. TMSCl (2 eq) 2. i. *t*-BuLi (2.2 eq), Et_2O, -78 °C ii. $B(OMe)_3$ (xs), -78 °C iii. 0.1N aq. HCl	 (45%)	183
2		i. MeMgCl (5 eq) THF, 0 °C ii. *t*-BuLi (5 eq), -78 °C iii. $B(OMe)_3$ (10 eq), 0 °C	 (80%)	184
3		i. *n*-BuLi (2 eq) Et_2O, 0 °C, 2 h; -78 °C ii. $B(OMe)_3$ (1 eq) iii. aq. HCl	 (86%)	18
4		i. *i*-PrMgBr, THF, -40 °C ii. $B(OMe)_3$, THF, -78 °C iii. $HOCH_2CH_2OH$, toluene	 (85%)	186
5		i. *t*-BuLi, THF, -78 °C ii. 	 (68%)	187
6		i. s-BuLi, TMEDA THF, -78 °C ii. $B(OMe)_3$ ii. 5% aq. HCl	 (80%)	192
7		i. s-BuLi, TMEDA THF, -78 °C ii. $B(OMe)_3$ ii. 5% aq. HCl		193
8		i. *n*-BuLi (1 eq) THF, < -20 °C ii. $B(O\text{-}i\text{-}Pr)_3$ (1.3 eq) ii. *i*-PrOH-NH_4Cl-H_2O	 (89%)	195

Table 1.3 Continued

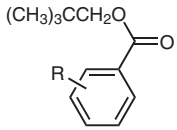
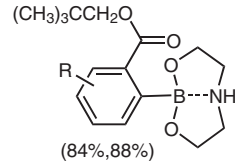
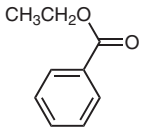
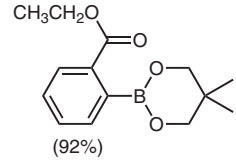
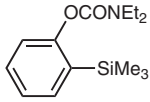
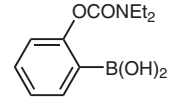
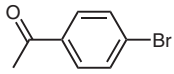
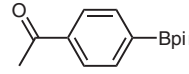
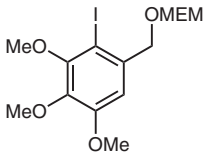
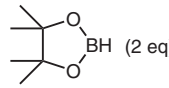
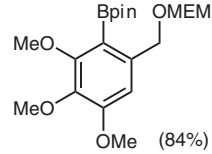
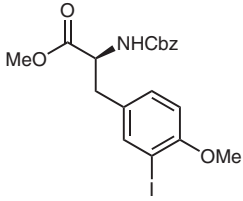
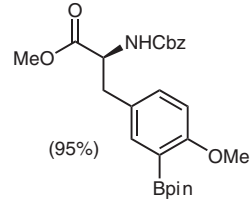
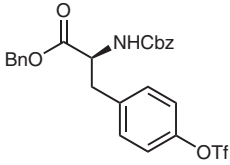
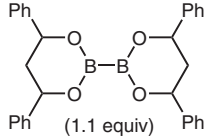
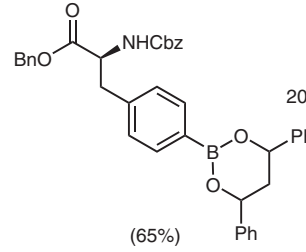
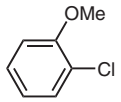
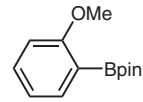
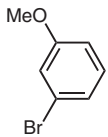
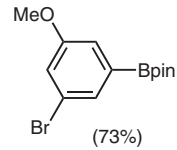
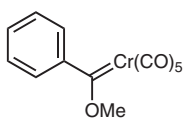
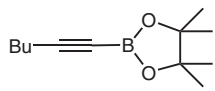
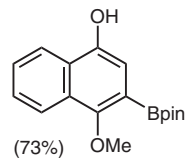
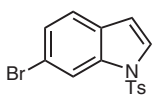
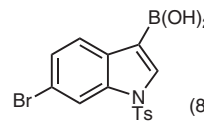
Entry	Substrate	Conditions	Product	Reference
9	 R = *p*-Br or *o*-Br	i. LDA (1.2 eq) B(O-*i*-Pr)$_3$ (2.6 eq), THF ii. diethanolamine (1.1 eq)	 (84%,88%)	196
10		i. LTMP (1.5 eq) B(O-*i*-Pr)$_3$ (2 eq) THF, -78 °C ii. $HOCH_2CMe_2CH_2OH$	 (92%)	197
11		i. BBr_3 (1.5 eq) CH_2Cl_2, -78 °C to RT ii. 5% aq. HCl	 (>85%)	193
12		B_2pin_2 (1.1 eq) $PdCl_2$(dppf) (3 mol%) KOAc (3 eq), DMSO, 80 °C, 1 h	 (80%)	200
13		 (2 eq) Et_3N (3 eq) $Pd(OAc)_2$ (5 mol%) PCy_2(o-biph) (10 mol%) 80 °C, 0.5 h	 (84%)	202
14		B_2pin_2 $PdCl_2$(dppf) (3 mol%) KOAc (3 eq), DMSO, 80 °C, 3 h	 (95%)	205
15		 (1.1 equiv) $PdCl_2$(dppf) (8 mol%) KOAc, DMF, 100 °C, 3 h	 (65%)	206

Table 1.3 Continued

Entry	Substrate	Conditions	Product	Reference
16		B_2pin_2 (1.1 eq) $Pd(dba)_2$ (3 mol%) PCy_3 (7.2 mol%), KOAc (1.5 eq) dioxane, 80 °C, 48 h	 (70%)	207
17		B_2pin_2 (1.1 eq) 1/2[IrCl(COD)]$_2$ + bpy (3 mol%) benzene, 80 °C, 16 h	 (73%)	213
18		 THF, 45 °C, 16 h	 (73%)	217
19		1. $Hg(OAc)_2$, AcOH, H_2O, $HClO_4$ 2. BH_3-THF 3. H_2O	 (85%)	187

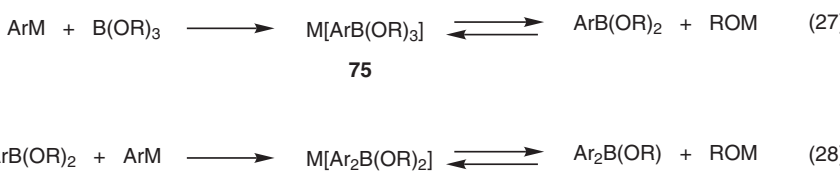


Figure 1.19 Equilibrium involved in the reaction between arylmetal intermediates (Li or Mg) and borates.

Isolation of free boronic acids using an aqueous work up may lead to low yields, especially for small or polar ones, which tend to be water-soluble even at a low pH (Section 1.4). In such cases, it is often better to isolate the desired boronic acid as an ester. In an improved procedure that does not involve an aqueous work-up, Brown and Cole reported that the reaction of several types of organolithium intermediates with triisopropylborate was very effective for the synthesis of arylboronic esters [180]. To help minimize the possible formation of borinic acids and boranes by multiple displacements (i.e., Equation 28 in Figure 1.19), the reaction protocol involves the slow addition of the organolithium to a solution of triisopropylborate in diethyl ether cooled to –78 °C. The use of smaller borate esters such as trimethylborate gave large proportions of multiple addition products (i.e., borinic acid and borane). With triiso-

propylborate, however, the clean formation of lithium alkoxyboronate salt (**75**, M = Li, R = *i*-Pr, Figure 1.19) was demonstrated by NMR spectroscopy, and the boronic ester can be obtained in high purity as the final product upon addition of anhydrous hydrogen chloride at 0 °C. An improvement to this procedure involves pyrolysis or the use of acid chlorides to breakdown the lithium triisopropylboronate salt, thereby avoiding the generation of free isopropanol and lithium chloride and facilitating the isolation of the boronic ester [181]. Recently, an "in-situ" quench variant whereby triisopropylborate is present in the flask prior to the addition of butyllithium was described; in many cases this simpler procedure afforded higher yields of aryl- and heteroaryl boronic acids compared to the sequential addition procedure [182]. Provided the requisite aryllithium reagent is readily accessible, all these procedures provide the corresponding isopropyl boronic esters in high yields. In addition to arylboronic esters, alkenyl, alkynyl, alkyl and even (α-haloalkyl)boronic esters were made this way [180]. If so desired, the free boronic acid may be obtained by hydrolysis of the ester. The metal–halogen exchange route can even be applied to functionalized substrates containing acidic hydrogen atoms, provided either temporary protection is effected (entry 1, Table 1.3) or a suitable excess of organometallic reagent is employed (entries 2 and 3). All isomers of hydroxybenzeneboronic acid were synthesized from the corresponding bromophenols using this method [185].

Recently, a new convenient procedure to synthesize arylboronic esters from Grignard reagents and trimethylborate was described [186]. This method involves a nonaqueous workup procedure in which the resulting solution of aryldimethoxyboronate is evaporated to eliminate the excess $B(OMe)_3$, and the residual solid is refluxed overnight in a solution of diol in toluene. In particular, several examples of ethylene glycol arylboronic esters were described with this method (e.g., entry 4, Table 1.3). Alternatively, the robust pinacol ester can be obtained directly by electrophilic quench of the aryllithium intermediate with a pinacol borate ester (entry 5). The use of bis(diisopropylamino)boron chloride as trapping agent in the reaction of both organolithium and magnesium compounds provides the corresponding bis(diisopropylamino)boranes, which can be easily transformed into the corresponding boronic esters and oxazaborolidines by exchange with a diol or an aminodiol [188].

1.3.1.1.2 By Directed ortho-Metallation

The metallation of arenes functionalized with coordinating ortho-directing groups such as amines, ethers, anilides, esters and amides is yet another popular way to access arylmetal intermediates that can be trapped with borate esters. Early work showed the suitability of ortho-lithiation of N,N-dialkylated benzylamines in the synthesis of *ortho*-methylamino-benzeneboronic acids [189–191]. Sharp and Snieckus further demonstrated the efficiency of this method in the preparation of *ortho*-carboxamido phenylboronic acids (entry 6, Table 1.3) [192]. This protocol was then generalized to many other substrates. For example, methoxymethoxybenzene (entry 7) and pivaloylaniline were treated with *s*-BuLi in the presence of TMEDA in THF at –78 °C, and the resulting ortho-lithiated intermediates quenched with trimethyl borate followed by an aqueous acidic workup described above (Section 1.3.1.1.1), to give the corresponding arylboronic acids in good yields [193, 194]. Although the crude

boronic acids could be used directly in Suzuki cross-coupling reactions, they were characterized as their stable diethanolamine adducts. The ortho-metallation route to arylboronic acids constitutes a reliable process in pharmaceutical chemistry where it can be applied to heterocyclic intermediates such as a tetrazole required in the synthesis of the antihypertensive drug Losartan (entry 8, Table 1.3) [195]. The use of esters as directing groups is more problematic as the metallated intermediate can undergo condensation with the benzoate substrate, giving a benzophenone. In one protocol, the metallation step is performed in the presence of the electrophile [196]. This in situ metallation-boronylation procedure employs LDA as base, and neopentyl esters were found to be particularly suitable because of their stability in the presence of this base. Most importantly, LDA is compatible with borate esters under the conditions employed, and its inertness to bromide-substituted benzoates provides another significant advantage over the use of BuLi for the deprotonation step. Thus, a solution of bromo-substituted neopentyl benzoate esters and excess triisopropylborate treated with LDA (1.1–1.5 equiv.) in THF led to the isolation of crude *ortho*-carboxy arylboronic acids, which were isolated as diethanolamine adducts in high yields (entry 9, Table 1.3). A limitation of this method using LDA as base is the requirement for an electron-withdrawing substituent to activate the arene substrate. Neopentyl benzoate, for example, does not undergo directed metallation and gives, rather, the corresponding diisopropyl carboxamide. A recent variant of this in situ trapping procedure using 2,2,6,6-tetramethylpiperidide (LTMP) as the base led to a more general methodology, allowing the presence of other substituents normally incompatible with standard ortho-metallation procedures with alkyllithium bases [197]. For example, ethyl benzoate, benzonitrile, fluoro- and chlorobenzene were transformed in high yield into the corresponding ortho-substituted boronic acids as neopentylglycol esters. As demonstrated in particular in the case of ethyl benzoate (entry 10), the use of LTMP as base is quite advantageous because LDA fails to metallate this substrate and provides instead the carboxamide product of addition to the ester.

1.3.1.2 **Transmetallation of Aryl Silanes and Stannanes**

One of the earliest methods for preparing aromatic boronic acids involved the reaction between diaryl mercury compounds and boron trichloride [198]. As organomercurial compounds are to be avoided for safety and environmental reasons, this old method has remained unpopular. In this respect, trialkylaryl silanes and stannanes are more suitable and both can be transmetallated efficiently with a hard boron halide such as boron tribromide [199]. The apparent thermodynamic drive for this reaction is the higher stability of B–C and Si(Sn)–Br bonds of product compared to the respective B–Br and Si(Sn)–C bonds of substrates. Using this method, relatively simple arylboronic acids can be made following an aqueous acidic workup to hydrolyze the arylboron dibromide product [193]. For example, some boronic acids were synthesized more conveniently from the trimethylsilyl derivative than by a standard ortho-metallation procedure (entry 11, Table 1.3).

1.3.1.3 Coupling of Aryl Halides with Diboronyl Reagents

The traditional method involving the trapping of aryllithium or arylmagnesium reagents with borate esters is limited by the functional group compatibility of these hard organometallic species as well as the rigorously anhydrous conditions required. In search of milder conditions amenable to a wider scope of substrates and functionalities, Miyaura and co-workers found that diboronyl esters such as B_2pin_2 (**58**, Figure 1.14) undergo a smooth cross-coupling reaction with aryl bromides, iodides, and triflates under palladium catalysis [200]. This new reaction process is described in Chapter 2; thus only a brief summary is presented here. A detailed mechanism has been proposed [139b, 200], and several diboronyl reagents are now commercially available, including diborylpinacolate (B_2pin_2). Despite the obvious appeal of this cross-coupling method [139], the prohibitive price of the diboronyl reagents currently restrains its use for the large-scale preparation of boronates. Standard conditions for the coupling reaction involve $PdCl_2$(dppf) as catalyst, with potassium acetate as the base in a polar aprotic solvent [200]. The mildness of these conditions is evidenced by the use of carbonyl-containing substrates such as benzophenones (entry 12, Table 1.3) or benzaldehydes [83], which would be unsuitable in the Brown–Cole procedure using organolithium intermediates. The cheaper reagent pinacolborane (**53**, Figure 1.13) can also serve as an efficient boronyl donor in this methodology (entry 13) [201]. Cedranediolborane has also been proposed as an alternative to pinacolborane, which gives pinacol esters that are notoriously difficult to hydrolyze (Section 1.2.3.2.2) [203]. The scope of haloarene substrates in coupling reactions with diboronyl esters or pinacolborane is very broad. A recent example described the preparation of peptide dimers using a one-pot borylation/Suzuki coupling [204]. Hindered or electron-rich aryl halides may also be used with high efficiency (entries 13, 14, Table 1.3). Of particular significance is the use of pinacolborane with aryltriflates, which can be made with ease from phenols [201]. For instance, 4-borono-phenylalanine is now easily accessible from tyrosine using this approach (entry 15). This example also shows that the use of diboronyl reagents with hydrolytically labile substituents is advantageous if the desired product is the free boronic acid. Aryl chlorides are more attractive substrates than bromides and iodides due to their low cost and wider commercial availability. In this regard, the development of modified conditions with $Pd(dba)_2$ and tricyclohexylphosphine as catalyst system has expanded the scope of this coupling methodology to aryl chlorides – even electron-rich ones (entry 16, Table 1.3) [207]. Alternatively, a microwave-promoted procedure for aryl chlorides using a palladium/imidazolium system has been described [208]. Recently, a similar procedure employed aryldiazonium salts as substrates [209].

1.3.1.4 Direct Boronylation by Transition Metal-catalyzed Aromatic C–H Functionalization

In terms of atom-economy, a very attractive strategy for accessing arylboronic acids is the direct boronylation of arenes through a transition metal promoted C–H functionalization. In addition to the catalyst, a suitable boron donor is required, and both diboronyl esters and dialkoxyboranes are very appropriate in this role. The concept of this type of direct borylation was first demonstrated on alkanes using photochemical

conditions [210]. For arene substrates, several research groups, including those of Smith [211], Hartwig [212], Miyaura/Hartwig [213] and Marder [214] have recently reported a number of efficient procedures using iridium and rhodium catalysts (entry 17, Table 1.3). This new reaction process has also generated much interest for its mechanism [215]. Regioselectivity remains a major challenge in aromatic C–H activation with mono- and polysubstituted arenes, and, not surprisingly, new advances are reported at a rapid pace [216]. This recent and emerging approach to the synthesis of boronic acid derivatives is discussed in detail in Chapter 2.

1.3.1.5 Other Methods

Harrity and co-workers described the application of 2-substituted 1-alkynylboronic esters in the Dötz cycloaddition of Fisher chromium carbene complexes, affording in a highly regioselective fashion a novel class of hydroxy-naphthyl boron pinacolates (entry 18, Table 1.3) [217]. These reaction products also provided, upon treatment with ceric ammonium nitrate, the corresponding quinone boronic esters.

1.3.2 Diboronic Acids

The preparation of all three substitution patterns of benzenediboronic acid has been reported (Figure 1.20). Whereas the preparation of the 1,4- and 1,3-benzenediboronic acids **76** and **77** from the corresponding dibromides were well described [157a, 218], that of the ortho isomer **78** is more tedious [72, 219]. Several other mono- and polycyclic aromatic diboronic acids, such as **79** [150], **80** [220], and **81** [221], have been described.

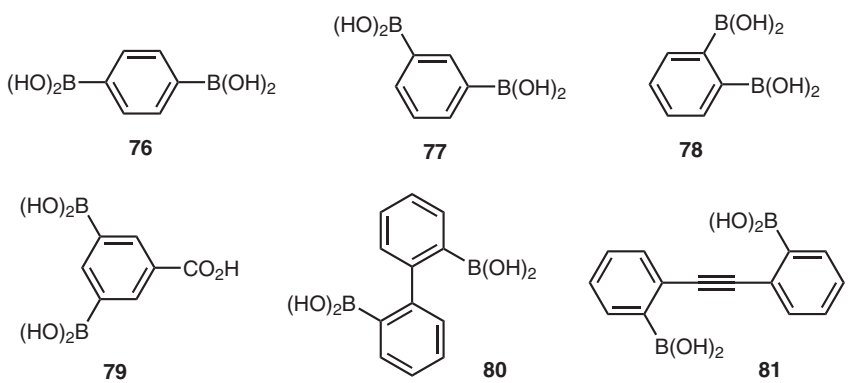


Figure 1.20 Selected examples of diboronic acids.

1.3.3
Heterocyclic Boronic Acids

Heterocyclic aromatic boronic acids, in particular pyridinyl, pyrrolyl, indolyl, thienyl, and furyl derivatives, are popular cross-coupling intermediates in natural product synthesis and medicinal chemistry. The synthesis of heterocyclic boronic acids has been reviewed recently [222], and will not be discussed in detail here. In general, these compounds can be synthesized using methods similar to those described in the above section for arylboronic acids. Of particular note, all three isomers of pyridineboronic acid have been described, including the pinacol ester of the unstable and hitherto elusive 2-substituted isomer, which is notorious for its tendency to protodeboronate [223]. Improvements and variants of the established methods for synthesizing heterocyclic boronic acids have been constantly reported [13, 182]. For example, a Hg-to-B transmetallation procedure was recently employed to synthesize a highly functionalized indolylboronic acid (entry 19, Table 1.3) [187].

1.3.4
Alkenylboronic Acids

Alkenylboronic acids constitute another class of highly useful synthetic intermediates. They are particularly popular as partners in the Suzuki–Miyaura cross-coupling reaction for the synthesis of dienes and other unsaturated units present in many natural products (Section 1.5.3.1). Several methods are available for the synthesis of a wide range of alkenylboronic acids with different substitution patterns. These approaches are summarized in Figure 1.21 and are described in the sub-sections below.

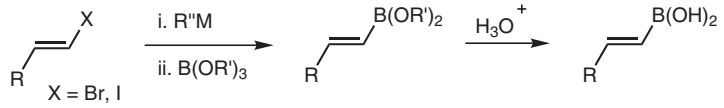
1.3.4.1 Electrophilic Trapping of Alkenymetal Intermediates with Borates

Alkenylboronic acids can be synthesized from reactive alkenylmetal species in a way similar to that described above for arylboronic acids (Section 1.3.1.1.1) [224]. Typically, alkenyl bromides or iodides are treated sequentially with *n*-BuLi and a trialkylborate (entry 1, Table 1.4). A nonpolar trienylboronic acid was synthesized using this approach [226]. As described in Section 1.2.2.2, small boronic acids tend to be highly soluble in water and may be difficult to isolate when made using the traditional approach involving an aqueous workup. In these cases, exemplified with the polymerization-prone ethyleneboronic acid synthesized from vinylmagnesium bromide, it has proved more convenient to isolate the product as a dibutyl ester by extraction of the acidic aqueous phase with butanol [227]. Recently, alkoxy-functionalized butadienyl- and styrenyl boronic esters were synthesized from α,β-unsaturated acetals by treatment with Schlosser's base and subsequent trapping with triisopropylborate (entry 2) [228].

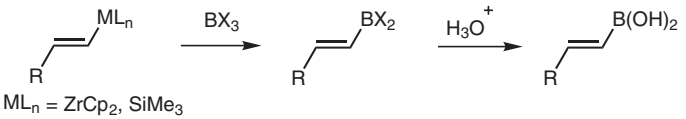
1.3.4.2 Transmetallation Methods

The treatment of trialkylsilyl derivatives with boron halides described in Section 1.3.1.2 is applicable to alkenyltrimethylsilanes [229]. It was employed as a method for

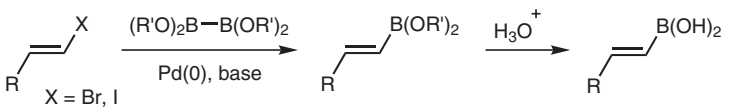
1.3.4.1 Electrophilic trapping of alkenylmetal intermediates with borates



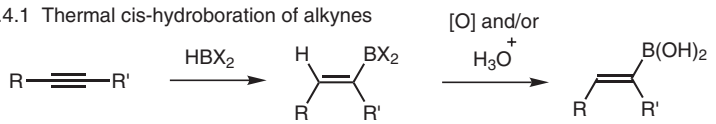
1.3.4.2 Transmetallation methods



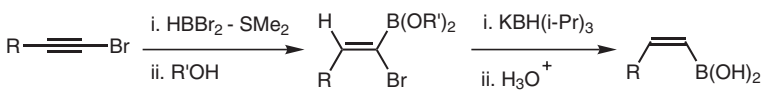
1.3.4.3 Transition metal catalyzed coupling between aryl halides/triflates and diboronyl reagents



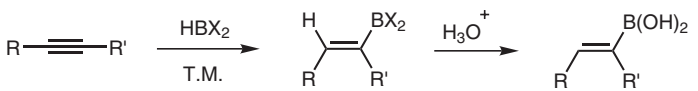
1.3.4.4.1 Thermal cis-hydroboration of alkynes



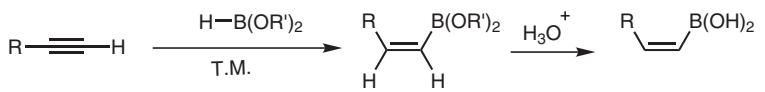
1.3.4.4.2 Indirect trans-hydroboration using alkynyl bromides



1.3.4.4.3 Transition metal-catalyzed cis-hydroboration of alkynes



1.3.4.4.4 Rhodium and iridium catalyzed trans-hydroboration of alkynes



1.3.4.5 Alkene metathesis

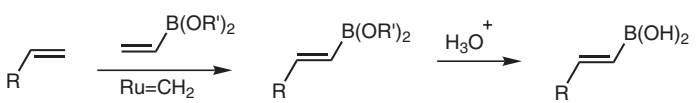


Figure 1.21 Common methods for the synthesis of alkenylboronic acids (esters).

Table 1.4 Selected examples of preparative methods for alkenylboronic acids and esters. pin = pinacolato ($OCMe_2CMe_2O$), cat = catecholato

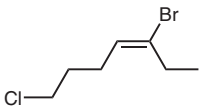
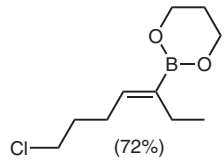
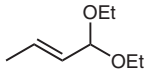
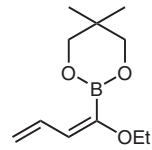
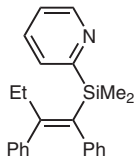
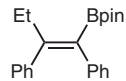
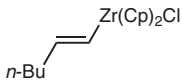
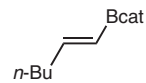
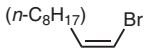
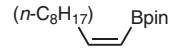
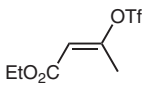
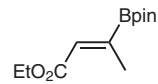
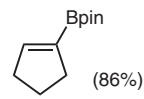
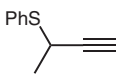
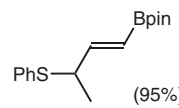
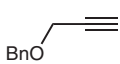
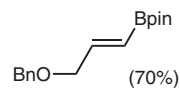
Entry	Substrate	Conditions	Product	Reference
1		i. *s*-BuLi, THF, -78 °C ii. $B(OR')_3$, -78 °C, 1 h iii. HCl/Et_2O, -78 °C to rt iv. H_2O v. $HO(CH_2)_3OH$	 (72%)	225
2		i. *n*-BuLi/KO-*t*-Bu (2.5 eq), THF, -95°C, 2 h ii. $B(O\text{-}i\text{-}Pr)_3$ (2 eq) -95 °C to rt iii. H_2O, extraction iv. $HOCH_2CMe_2CH_2OH$ (1 eq) toluene, rt, 12 h	 (93%)	228
3		1. BCl_3 (2.2 eq) CH_2Cl_2, -40 °C, 5 h 2. pinacol, Et_3N	 (82%, *Z*/*E* 98:2))	231
4		catBCl CH_2Cl_2, 0 °C	 (57%)	232
5		B_2pin_2 (1.1 eq) $PdCl_2(dppf)$ (3 mol%) PPh_3 (6 mol%) KOPh (1.5 eq), toluene, 50 °C, 5 h	 (74%)	234
6		B_2pin_2 (1.1 eq) $PdCl_2(PPh_3)_2$ (3 mol%) PPh_3 (6 mol%) KOPh (1.5 eq), toluene, 50 °C, 1 h	 (93%, >99% Z:E)	235
7		HBpin (1.5 eq) $PdCl_2(dppf)$ (3 mol%) $AsPh_3$ (12 mol%), Et_3N (3 eq), dioxane, 80 °C, 16 h	 (86%)	236
8		i. Cy_2BH (1 eq), DME, rt, 1 h ii. Me_3NO (2 eq), reflux iii. $HOCMe_2CMe_2OH$ (1 eq), rt, 12 h	 (95%)	244
9		i. Cy_2BH (1 eq), DME, rt, 1 h ii. Me_3NO (2 eq), reflux iii. $HOCMe_2CMe_2OH$ (1 eq), rt, 12 h	 (70%)	244

Table 1.4 Continued.

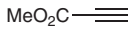
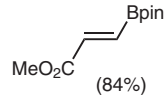
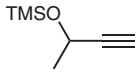
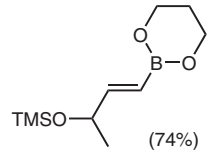
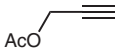
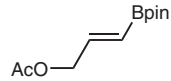
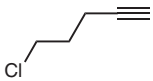
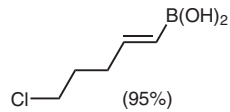
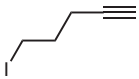
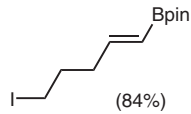
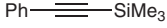
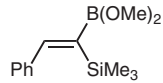
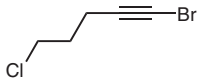
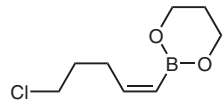
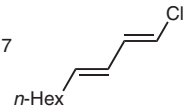
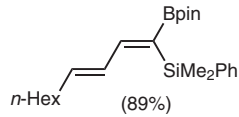
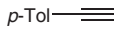
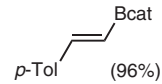
Entry	Substrate	Conditions	Product	Reference
10		i. Ipc_2BH, THF, -35 °C to 0 °C ii. CH_3CHO (10 eq), 0 to 40 °C iii. $HOCMe_2CMe_2OH$ (1 eq), rt, 12 h	 (84%)	246
11		i. Ipc_2BH, THF, -35 °C to rt, 5 h ii. CH_3CHO (xs), 0 °C; reflux 12 h iii. $HO(CH_2)_3OH$	 (74%)	247
12		i. **87** (1 eq) ii. H_2O, rt, 0.5 h iii. aq. CH_2O (1 eq), rt, 1 h iv. $HOCMe_2CMe_2OH$ (1.1. eq), rt, 12 h	 (55%, 97:3 regio)	248
13		i. CBH (1 eq), 70 °C, 1 h ii. H_2O, 25 °C, 1 h iii. filtration	 (95%)	249b
14		HBpin (2 eq), CH_2Cl_2, 25 °C, 6 h	 (84%)	134
15		i. $HBCl_2$ (1 eq), BCl_3 (1 eq) pentane, -78 °C; rt, 12 h ii. MeOH, Et_3N, 0 °C	 (46%)	253
16		i. $HBBr_2$-SMe_2, CH_2Cl_2 ii. MeOH, pentane iii. $K(i\text{-}PrO)_3BH$, Et_2O, 0 °C to rt, 0.5 h iv. H_2O, 0 °C v. $HO(CH_2)_3OH$	 (89%)	256
17		i. *n*-BuLi (1.05 eq), THF, -90 °C, 15 min ii. $PhMe_2SiB(OCMe_2)_2$, warm up to rt, 12 h	 (89%)	259
18		HBcat (1 eq), $Cp_2Ti(CO)_2$ (4 mol%) C_6H_6, 25 °C, 2 h	 (96%)	262

Table 1.4 Continued.

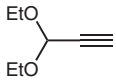
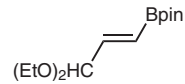
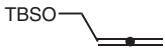
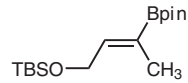
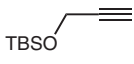
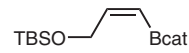
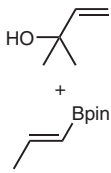
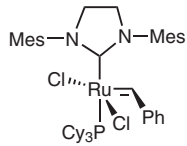
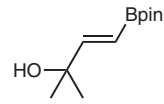
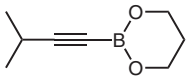
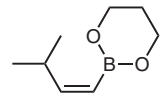
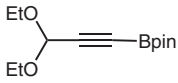
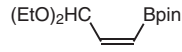
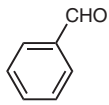
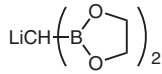
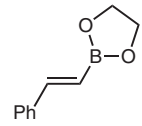
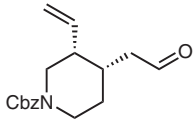
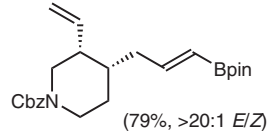
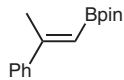
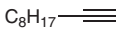
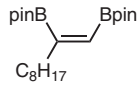
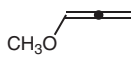
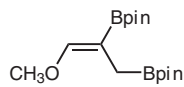
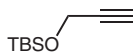
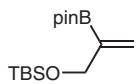
Entry	Substrate	Conditions	Product	Reference
19		HBpin (1.05 eq), $HZrCp_2Cl$ (5 mol%) CH_2Cl_2, 25 °C, 24 h	 (82%)	263
20		HBpin (1.5 eq) $Pt(dba)_2$ (3 mol%) $P(t\text{-}Bu)_3$ (6 mol%) toluene, 50 °C, 2 h	 (82%)	267
21	 (1.2 eq)	HBcat (1 eq) $[Rh(cod)Cl]_2$ (1.5 mol%) PPr_3 (6 mol%) Et_3N (1 eq) cyclohexane, rt, 2 h	 (71%, 99% *Z*)	268
22	 (1 equiv each)	 (5 mol%) CH_2Cl_2, reflux	 (61%, > 20:1 E:Z)	272
23		i. H_2, Lindlar, pyridine 1,4-dioxane, rt, 1.5 h ii. H_2O iii. $HO(CH_2)_3OH$, pentane	 (83%, 95% *Z*)	276
24		i. $HZrCp_2Cl$ (1.2 eq) THF, 25 °C, 0.5 h ii. H_2O, 0.5 h	 (82%)	277
25		 THF/CH_2Cl_2 -78 °C, 3 h	 (87%, >93% *E*)	279
26		$Cl_2CHBpin$ (2 eq) $CrCl_2$ (8 eq) LiI (4 eq) THF, 25 °C	 (79%, >20:1 *E*/*Z*)	284

Table 1.4 Continued.

Entry	Substrate	Conditions	Product	Reference
27		trans-[RhCl(CO)(PPh_3)$_2$] (5 mol%) B_2pin_2 (0.67 eq) 3:1 toluene-CH_3CN, 80 °C, 3 d	 (90%)	286
28	 (1.1 equiv)	B_2pin_2 (1 eq) Pt(PPh_3)$_4$ (3 mol%) DMF, 80 °C, 24 h	 (86%)	288
29	 (1.5 equiv)	B_2pin_2 (1 eq) Pt(dba)$_2$ (10 mol%) PCy_3 (10 mol%) toluene, 50 °C, 18 h	 (85%)	290
30		B_2pin_2 (1.1 eq) CuCl (1.1 eq) KOAc (1.1 eq) P(*t*-Bu)$_3$ (1.1 eq) DMF, rt, 16 h	 (62%, 91:9 regiosel.)	291

preparing ethylene boronic esters [230]. Recently, isomerically pure tetrasubstituted alkenylboronic esters were synthesized by this approach, following an esterification of the intermediate dichloroborane with pinacol (entry 3, Table 1.4) [231]. *trans*-Alkenylboronic acids can also be synthesized from zirconocene intermediates obtained from the hydrozirconation of terminal alkynes (entry 4) [232].

1.3.4.3 Transition-metal Catalyzed Coupling between Alkenyl Halides/Triflates and Diboronyl Reagents

Alkenyl halides and triflates are suitable substrates in the palladium-catalyzed borylation reaction described above for aromatic substrates (Section 1.3.1.3). In this reaction, the geometry of the starting alkenyl halide is preserved in the product, and several functionalities are tolerated in the substrate. At the outset, however, Miyaura and co-workers found that the conditions utilized for aryl halide substrates led to low yields of the desired alkenylboronate due to competing reactions such as the formation of the homo-coupled product of Suzuki cross-coupling [233]. To improve the rate of transmetallation between the diboronyl reagent (B_2pin_2) and the oxidative addition Pd(II) intermediate, stronger bases were evaluated. In the optimal procedure, potassium phenoxide was the most effective base, with a less polar solvent (toluene) than that used with aryl halides, and triphenylphosphine as ligand in place of dppf. Alkenyl bromides and triflates were superior to iodides, and generally afforded good yields of products (70–90%). The mildness of these conditions opened up a rather

impressive scope of suitable substrates [234], including (*Z*)-alkenes (entry 5, Table 1.4), and both acyclic and cyclic ones with functionalities such as alkyl halides, silyl-protected alcohols, and carboxylic esters (entry 6) [235]. Pinacolborane was effective in the borylation of alkenyl halides under a new set of optimal conditions (entry 7) [236]. No competing hydroboration was observed, but *Z*-configured substrates are inverted under these reaction conditions.

1.3.4.4 **Hydroboration of Alkynes**

1.3.4.4.1 Thermal cis-Hydroboration

Since its discovery by Brown and Rao in 1956 [237], hydroboration chemistry has been a central reaction in the preparation of organoboron compounds [238]. cis-Hydroboration of terminal alkynes provides ready access to *trans*-2-substituted alkenylboronic acids [239], and several borane reagents have been used for this purpose (Figure 1.22). Non-differentiated internal alkynes usually give mixtures of regioisomeric alkenylboron compounds. With terminal alkynes, however, the hydroboration is highly regioselective and adds boron at the terminal carbon. Likewise, whereas small borane reagents tend to undergo a double hydroboration of the alkyne substrate, more hindered boranes allow the hydroboration process to stop with ease after one addition, avoiding further hydroboration of the desired product into a diboroalkane [239]. Thus, the bulky dialkylborane reagents disiamylborane (**82**) [239], thexylborane (**83**) [240], dicyclohexylborane (**84**) [241], and 9-BBN (**85**) [242] all react with terminal alkynes to provide 2-substituted dialkylalkenylboranes in a very high regioselectivity. The corresponding alkenylboronic acid may be obtained after an appropriate oxidative workup, which is generally performed with a mild and selective oxidant for the two sp^3 C–B bonds. To this end, trimethylamine oxide was found most suitable [243], leaving not only the alkenyl boron–carbon bond intact but also a selenide and a sulfide substituent (entry 8, Table 1.4) [244]. In the hydrolysis of the resulting alkenylboronate, the ensuing separation of the desired boronic acid from the alcohol by-product originating from the oxidation of the dialkylborane is not always straightforward. Hoffmann and Dresely described a procedure with dicyclohexylborane in which the boronic acid is esterified in situ as a pinacolate after the oxidation step, then purified by distillation to eliminate the residual cyclohexanol [244]. This way, several functionalized (*E*)-1-alkenylboronates were isolated – the use of DME, a polar coordinating solvent, was essential when using a propargylic ether as substrate (entry 9). Otherwise, no reaction occurred, possibly due to the coordination of Cy_2BH to the basic ether. For substrates that may be sensitive to the oxidative workup, or to avoid the cyclohexanol by-product, diisopinocampheylborane (**86**, Figure 1.22) [245] offers a milder alternative. With this reagent, the alkyne is hydroborated and then subjected to a gentle oxidative dealkylation using acetaldehyde to afford a diethyl alkenylboronic ester along with two equivalents of pinene [246, 247]. The crude diethyl alkenylboronate can be transesterified with diols such as pinacol to yield the corresponding pinacol ester, which in most cases must be purified by distillation or chromatography. Although several highly functionalized alkenylboronates were synthesized using this method (entries 10 and 11), it is often difficult to completely elim-

inate the pinene by-product by distillation. Recently, the new reagent di(isopropylprenyl)borane, **87**, was described [248]. Much like reagent **86**, it features a mild neutral workup, which can be done with aqueous formaldehyde or water (entry 12).

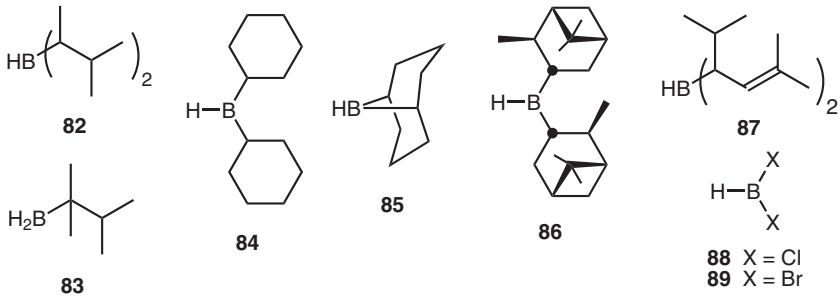


Figure 1.22 Common hydroborating agents for alkynes.

The use of 4,4,6-trimethyl-1,3,2-dioxaborinane (**51**, Figure 1.13) [132], catecholborane (**52**) [249], pinacolborane (**53**) [134], or the more reactive 1,3,2-dithiaborolane (**54**) [136] provides the boronic acid derivative directly after a hydrolytic workup with no oxidation step. Yet, these methods are not without disadvantages. Dialkoxyboranes are less reactive than the dialkylboranes described above. For example, alkyne hydroborations with catecholborane are often performed at temperatures as high as 100 °C. In this regard, dialkylboranes such as Cy_2BH were found to catalyze these hydroborations at room temperature [250]. Because dialkylboranes are more reactive than catecholborane, it was suggested that this catalytic process involves exchange of the resulting alkenyl group with catecholborane to recycle the dialkylborane. Moreover, although catecholborane was employed with highly functionalized substrates [251], it does not tolerate acetal or ether functionalities at the propargylic carbon [244, 247], and the acidic catechol released in the aqueous workup needs to be neutralized and removed from the mixture (entry 13). By producing the robust pinacolate ester in a single operation, the use of pinacolborane (**53**) is quite advantageous although the addition also tends to be sluggish (entry 14). Dibromoborane (**89**, Figure 1.22), in the form of a methyl sulfide complex, conveniently gives access to 1-alkenylboronic acids bearing alkyl or aryl substituents at the 2-position following alcoholysis of the intermediate alkenyldibromoborane [252]. Several other functionalities, however, are not well tolerated by this reagent. The related dichloloroborane (**88**) undergoes a regioselective hydroboration with silylacetylenes, giving the (*E*)-1-trimethylsilyl-1-alkenylboronic ester after methanolysis (entry 15) [253]. Dichloroborane is difficult to handle, but a simple variant, presumed to generate it in situ by reaction of trimethylsilane with boron trichloride, was also shown to hydroborate alkynes [254]. Alternatively, a recent report demonstrated the suitability of the stable and commercially available Cl_2BH–dioxane complex for the preparation of 1-alkenylboronic acids [255].

1.3.4.4.2 Indirect trans-Hydroboration using Alkynyl Bromides

All the above hydroboration methods provide terminal *trans*-alkenylboronic acids by a highly regioselective syn addition of the B–H bond across the terminal alkyne. To provide *cis*-alkenylboronic acids, Brown and Imai developed an ingenious two-step method based on the regioselective hydroboration of bromoalkynes with dibromoborane (Figure 1.21) [256]. In this procedure, the resulting (*Z*)-1-bromo-alkenyldibromoboranes are transformed into the corresponding esters through simple alcoholysis. The isolated boronates are then treated with potassium triisopropoxyborohydride (KIPBH) to effect a stereospecific bromide substitution by inversion of configuration, thereby affording the *cis*-alkenylboronic esters. Whereas dibromoborane presents a limited scope of chemoselectivity, KIPBH is relatively mild. For example, it tolerates a primary alkyl chloride on the substrate (entry 16, Table 1.4). Furthermore, an extension of this approach employing organolithium or Grignard reagents in place of KIPBH leads to the stereoselective preparation of (*E*)-1-substituted-1-alkenylboronic esters that could not obtained via the hydroboration of alkynes [257, 258]. Recently, a similar nucleophilic substitution mechanism has also been proposed in a new method involving the addition of alkenyllithium intermediates to the diboronyl reagent B_2pin_2 or the related dimethylphenylsilyl(pinacolato)borane [259]. In this reaction, which accomplishes a geminal difunctionalization of formal alkenylidene-type carbenoids, 1,1-diboronylalkenes or 1-silyl-1-alkenylboronates are produced (entry 17).

1.3.4.4.3 Transition Metal-catalyzed cis-Hydroboration

Since the discovery of the rhodium-catalyzed hydroboration of alkenes by Männig and Nöth in 1985 [260], this method has generally not provided satisfactory results when applied to alkynes [261]. Hartwig and He, however, found that dicarbonyltitanocene effectively catalyzes the hydroboration of alkynes with catecholborane without the contamination of by-products of catecholborane decomposition usually observed under rhodium catalysis (entry 18, Table 1.4) [262]. By taking advantage of the superior stability of pinacolborane over catecholborane, Pereira and Srebnik developed a very convenient zirconocene-catalyzed procedure for the pinacolboration of terminal alkynes (entry 19) [263]. This method, which features lower reaction temperature and times than the non-catalyzed variant of Knochel and co-workers [134], provides the (*E*)-1-alkenylboronates as their convenient pinacolate esters in high yields and regioselectivity. Other transition metal catalysts, such as $Rh(CO)(Ph_3P)_2Cl$ and $NiCp(Ph_3P)Cl$, are also effective in conjunction with pinacolborane as the hydroborating agent [264]. Like the non-catalyzed hydroboration, internal alkynes tend to give mixtures of regioisomers. Using thioalkynes, however, a nickel-catalyzed catecholboration method afforded the 2-alkylthio-1-alkenylboronates in high regioselectivity [265]. An early study described one example of $Pd(PPh_3)_4$-catalyzed catecholboration of an enyne to afford an allenylboronate [266].

Miyaura and co-workers also reported the $Pt(dba)_2$-catalyzed pinacolboration of terminal allenes; the regioselectivity was highly dependent on the nature of the added phosphine ligand [267]. For example, whereas the bulky tris(2,4,6-trimethoxyphenyl)phosphine often led to substantial amounts of the external Markovnikov prod-

uct, the use of tris(*t*-butyl)phosphine provided the internal hydroboration product as single isomer (entry 20, Table 1.4). Notably, the resulting 1-substituted-1-alkenylboronate would not be available using the uncatalyzed hydroboration of terminal allenes or terminal alkynes.

1.3.4.4.4 Rhodium- and Iridium-catalyzed trans-Hydroboration

Direct alkyne hydroboration methods, whether catalyzed or not, afford *trans*-alkenylboronic acids by a highly regioselective syn addition of the reagent's B–H bond across the terminal alkyne. The indirect Brown method to effect formal trans-hydroboration (Section 1.3.4.4.2) is limited by the need for a bromoalkyne and the harshness of the dibromoborane reagent employed. To fill this important methodological void and allow for a direct, mild formation of *cis*-alkenylboronic acids, Miyaura and co-workers sought a true "trans-hydroboration" method. They found that the hydroboration of alkynes with either catecholborane or pinacolborane in the presence of triethylamine and catalytic amounts of rhodium or iridium phosphine complex provides good to high yields of (*Z*)-1-alkenylboronic esters in a very high selectivity (entry 21, Table 1.4) [268]. Interestingly, deuterium-labeling experiments showed that the internal cis-hydrogen substituent comes from the terminal alkyne and not from the borane. Based on this information, a mechanism involving migration of the acetylenic hydrogen, and proceeding through a metal-vinylidene complex, was proposed to explain the selectivity of this unique "trans-hydroboration" method [268].

1.3.4.5 **Alkene Metathesis**

Recently, the advent of efficient catalysts for alkene metathesis has opened up new opportunities for the synthesis of alkenylboronic acids. For example, ring-closing metathesis of dienylboronic acids provides cyclic alkenylboronic acids that would be difficult to obtain otherwise [269]. Chemoselectivity in cross-metathesis chemistry is a significant problem that severely limits the synthesis of acyclic alkenes using these novel catalysts [270]. With most terminal alkenes, mixtures of disubstituted alkene products are obtained, and often with a low *E*/*Z* selectivity. Exceptionally, a number of alkene substrates are prone to undergo a highly chemoselective cross-metathesis with other terminal alkenes [270]. Fortunately, ethylene and 1-propenyl pinacol boronic esters are such favorable substrates [271, 272]. For example, Grubbs and coworkers discovered that the latter undergoes a clean cross-metathesis with terminal alkenes, catalyzed by a ruthenium alkylidene, to provide the (*E*)-1-alkenylboronic ester products in high selectivity (entry 22, Table 1.4) [272]. This methodology was tested in the synthesis of complex molecules such as epothilone analogues [273]. Ene-yne metathesis reactions based on alkynylboronic ester annulation strategies provide polysubstituted 2-butadienyl boronic esters [274, 275].

1.3.4.6 **Other Methods**

Though conceptually simple, photochemical *E* to *Z* isomerization of double bonds is not an efficient approach for accessing geometrically pure alkenylboronic esters [253, 258]. Alkynylboronic esters, however, can be selectively hydrogenated over Lindlar's catalyst [276]. 1,4-Dioxane was found to be the optimal solvent for providing (*Z*)-1-

alkenylboronates with stereochemical purity over 95% (entry 23, Table 1.4). Likewise, highly pure (*Z*)-1-alkenylboron pinacolates were isolated from the corresponding alkynylboronates and a sequence of regioselective hydrozirconation and aqueous protonolysis (entry 24) [277]. The synthesis of alkenylboronates using other types of additions and cycloadditions of alkynylboronates are described in Chapter 9.

Matteson and Majumdar have reported a Peterson-type olefination of the anion derived from a α-trimethylsilylmethylboronic ester ($LiCH(SiMe_3)Bpin$) [278]. Addition of the latter onto aldehydes provided the corresponding alkenylboronic esters as a mixture of geometrical isomers (~70:30 *Z*/*E*). No further optimization was reported towards controlling the *E*/*Z* selectivity in this potentially useful and unique method for synthesizing alkenylboronic acids from aldehydes. The corresponding lithiomethylenediboronic esters tend to provide mixtures favoring the *E* isomer (entry 25) [279, 280], and this approach to access alkenylboronic acids from aldehydes was employed in the total syntheses of natural products such as palytoxin [281] and the macrolide antibiotic rutamycin B [282]. A variant of the traditional Takai reaction, using $Cl_2CHBpin$, provides *trans*-1-alkenylboronic esters from aldehydes [283]; this procedure was recently employed in a synthesis of quinine (entry 26) [284].

Pinacol and 2-methyl-2,4-pentanediol esters of ethylene boronic acid are efficient substrates for Heck couplings with aryl and alkenyl halides, giving 2-aryl- and 2-butadienylboronates, respectively, with minimal side-product from Suzuki coupling [285]. Marder and co-workers have developed a dehydrogenative borylation of vinylarenes to access 2,2-disubstituted-1-alkenylboronates that are not accessible by standard alkyne hydroboration chemistry [286]. By using the catalyst precursor $RhCl(CO)(PPh_3)_2$ and B_2pin_2 or B_2neop_2, the authors found conditions that prevent significant competitive hydrogenation or hydroboration of the product. For example, (*E*)-Ph(Me)C=CH(Bpin) was obtained from α-methylstyrene in high yield and high geometrical selectivity (entry 27, Table 1.4). A mechanism that accounts for the beneficial role of acetonitrile as co-solvent was proposed. To access similar 2,2-disubstituted-1-alkenylboronates, a two-step sequence of bromoboration/Negishi coupling was described [287].

Diboronyl compounds add onto terminal and internal alkynes under platinum catalysis to provide *cis*-1,2-diboronylalkenes [288]. For example, $Pt(PPh_3)_4$ catalyzes the addition of bis(pinacolato)diboron (**58**) to 1-decyne, affording the corresponding alkenylbisboronate (entry 28, Table 1.4). Several other metal complexes tested, including palladium, rhodium and nickel complexes, failed to promote the same reaction. Mechanistically, the reaction's catalytic cycle is thought to be initiated by the oxidative addition of Pt(0) into the B–B bond, followed by a cis-boro-platination of the alkyne, and the cycle is terminated by the reductive elimination of the alkenyl-Pt(II)-Bpin unit to give the product and regenerate the Pt(0) catalyst [289]. Allenes also react similarly (entry 29) [290]. In a related process, B_2pin_2 was found to add to terminal alkynes at room temperature in the presence of stoichiometric copper(I) chloride and potassium acetate as the base [291]. It was proposed that a boron-to-copper transmetallation is involved, giving a putative boryl-copper species (CuBpin). The reaction provides a variable ratio of 1-boronyl and 2-boronyl alkenes, depending on the additive employed, which can either be a phosphine or LiCl (entry 30). Recently, Mu-

rakami and co-workers reported a palladium-catalyzed silaboration of allenes, affording 2-boronyl-allylsilanes [292]. The same group also described a palladium- and nickel-catalyzed intramolecular cyanoboronation of homopropargylic alkynes [293].

1.3.5
Alkynylboronic Acids

Like their aryl and alkenyl counterparts, alkynylboronic acids can be made by displacement of magnesium or lithium acetylides with borate esters. For example, Matteson and Peacock have described the preparation of dibutyl acetyleneboronate from ethynylmagnesium bromide and trimethyl borate [294]. The C–B linkage is stable in neutral or acidic hydrolytic solvents but readily hydrolyzes in basic media such as aqueous sodium bicarbonate. Brown and co-workers eventually applied their organolithium route to boronic esters to the particular case of alkynylboronic esters, and in this way provided a fairly general access to this class of compounds [295].

1.3.6
Alkylboronic Acids

Compared to aryl- and alkenylboronic acids, alkylboronic acids and esters have found limited use as synthetic intermediates aside for their oxidation into alcohols (Section 1.5.2.1). This is due in part to their inferior shelf-stability. In addition, their transmetallation with transition metal catalysts such as palladium is presumed to be more difficult than that of the unsaturated and aromatic boronic acid derivatives [296]. For example, alkylboronic acids have long been known to be reluctant substrates in the Suzuki-cross-coupling reaction, and they have become efficient in this application only very recently with the use of special bases and the advent of new and highly active catalyst systems (Section 1.5.3.1). Perhaps the most synthetically useful class of alkylboronic acids are the α-haloalkyl derivatives popularized by Matteson (Section 1.3.8.4), and their elegant chemistry is described in Chapter 8.

Alkylboronic acids and esters can also be synthesized from the trapping of organomagnesium and organolithium intermediates with borates. Methylboronic esters, for example, are made using the condensation of methyllithium and triisopropylborate [180]. Likewise, the useful α-chloromethylboronate reagents **90** can be made with the in situ trapping variant whereby butyllithium is added to a mixture of ICH_2Cl and triisopropylborate [297]. The corresponding bromides (**91**) [298] and iodides (**92**) [299] were also reported. Both catalyzed and uncatalyzed hydroboration of alkenes serve as powerful methods to access enantiopure alkylboronic esters. Because a selective oxidation of two of the resulting three B–C bonds following hydroboration with dialkylboranes is difficult, a hydroboration route to alkylboronic acids and esters is limited to reagents such as Ipc_2BH (**86**), dihaloboranes, and dialkoxyboranes (e.g., catechol- and pinacolborane). The asymmetric hydroboration of alkenes with Ipc_2BH or $IpcBH_2$ (Equation 29, Figure 1.23) [300, 301], or using chiral rhodium catalysts [302], constitutes well-established routes to access chiral alkylboronic esters or the corresponding alcohols or amines after a stereospecific oxidation of the B–C bond (Sec-

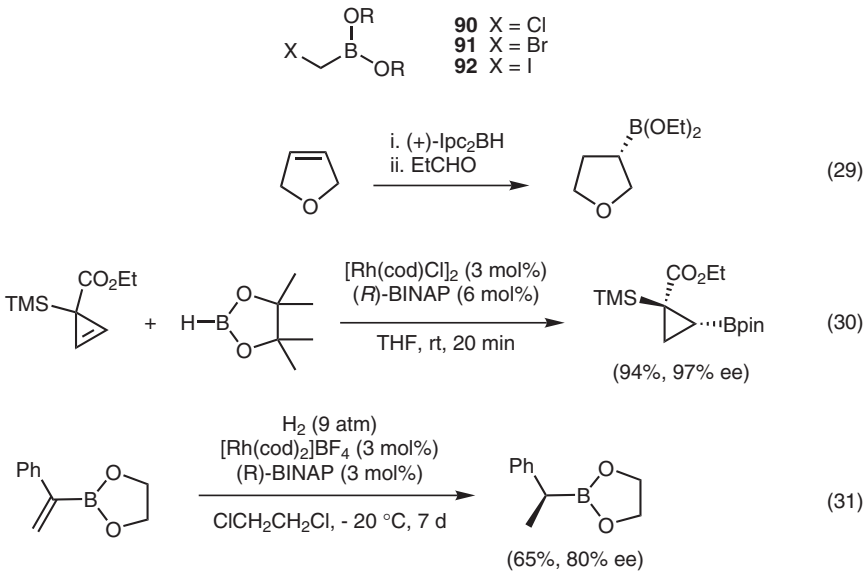
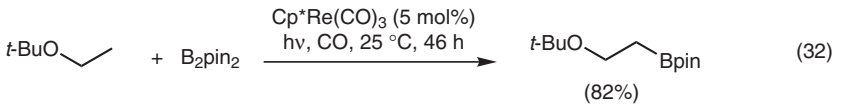


Figure 1.23 Alkylboronic acids (esters): selected examples of enantioselective preparative methods.

tions 1.5.2.1 and 1.5.2.2). Chiral cyclopropylboronic esters were obtained by catalytic enantioselective pinacolboration of cyclopropenes (Equation 30) [303]. Stereoisomerically pure alkylboronic esters can also be obtained through less common methods such as the hydrogenation of chiral alkenylboronic esters [304], and even with enantioselective variants using chiral catalysts (Equation 31) [305]. Other types of additions and cycloadditions of alkenylboronic esters are discussed in detail in Chapter 9. The aforementioned Matteson asymmetric homologation of (α-haloalkyl)boronic esters is another popular strategy to access new alkylboronic esters (Section 1.3.8.4 and Chapter 8). Alkylboronic acids have also been obtained by a regioselective rhenium-catalyzed C–H activation/boronylation reaction (Equation 32) [210b].

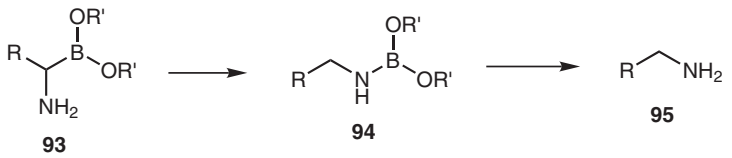


1.3.7
Allylic Boronic Acids

Because of their tremendous utility as carbonyl allylation agents (Section 1.5.3.2), several methodologies have been developed for synthesizing allylic boronic acids and their various esters. The preparation and reactions of allylic boronic esters are discussed in detail in Chapter 6.

1.3.8 Chemoselective Transformations of Compounds containing a Boronic Acid (Ester) Substituent

New boronic acid derivatives can be made by the derivatization of compounds that already contain a boronic acid(ester) functionality. The scope of possible transformations, however, relies on the compatibility of these reaction conditions with the boronate group, and in particular the oxidatively labile C–B bond. One seminal example illustrating the limitations imposed by the intrinsic reactivity of boronic acids is that of α-aminoalkylboronic acids, the boron analogues of amino acids (Section 1.3.8.4) [306]. The synthesis of these important derivatives remained an elusive goal for several years. The reason for the instability of compounds of type **93** is the incompatibility of free α-amino groups possessing hydrogen substituents, which undergo a spontaneous 1,3-rearrangement to give the homologated amine **94** (Equation 33) [111].



(33)

Eventually, this undesired process was prevented through rapid acetylation of the amino group or its neutralization as a salt [111]. This undesirable rearrangement was later exploited in a method for mono-N-methylation of primary amines [307]. As exemplified with the formation of ethylene by debromoboronation of 2-bromoethaneboronic acid, alkylboronic acids with a leaving group in the β-position are unstable under basic conditions [308]. Matteson has provided a detailed overview on the chemical compatibility of boronic acids and esters – a review that is undoubtedly of great help in avoiding trouble when derivatizing a boronic acid containing compound [309]. Therefore, only selected examples of boronate-compatible transformations are discussed in this section.

1.3.8.1 Oxidative Methods

The sensitivity of the B–C bond of boronic acids and esters to oxidation was discussed in Section 1.2.2.5.2. Although basic hydrogen peroxide and other strong oxidants rapidly oxidize B–C bonds, a certain degree of selectivity is possible. For example, sulfide and alcohol functionalities can be oxidized selectively without affecting the boronate group (Equations 34 and 35, Figure 1.24) [244]. However, epoxidation of alkenylboronic esters fails – but it can be achieved indirectly from trifluoroborates salts (Equation 26, Figure 1.17) [172]. The permanganate oxidation method is commonly employed to access carboxy-substituted arylboronic acids from methyl-substituted precursors [310]. Radical bromination of methyl-substituted arylboronic acids provides a route to the corresponding hydroxymethyl and formyl derivatives (Equations 36–38) [155]. Bromination of *p*-tolylboronic acid, followed by alkylation of aceta-

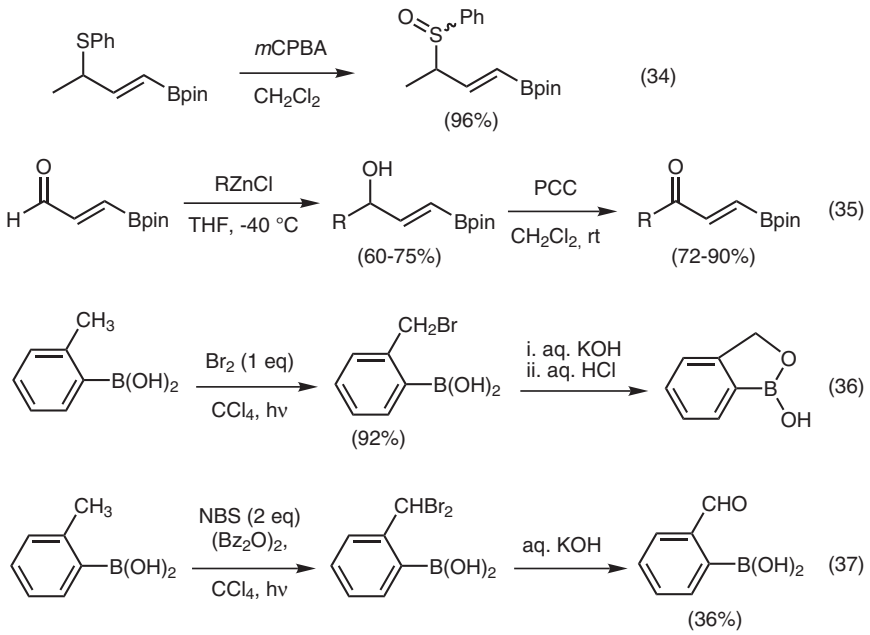


Figure 1.24 Chemoselective oxidation reactions involving boronic acid derivatives.

minomalonic ester, hydrolysis and decarboxylation, afforded the first synthesis of 4-borono-phenylalanine [155].

1.3.8.2 Reductive Methods

Care must be taken in using strong hydride reagents as they can transform boronic esters into dihydridoboranes (Section 1.2.3.6). Subsequent hydrolysis, however, can restore the boronic acid. Hindered alkenylboronates are tolerant of DIBALH (Scheme 1.3 below) [107]. Catalytic hydrogenation methods appear to be quite compatible with boronate groups, as shown by the examples of Figure 1.25 (Equations 38 and 39) [311, 312].

1.3.8.3 Generation and Reactions of α-Boronyl-substituted Carbanions and Radicals

Carbanions adjacent to a boronate group can be generated by two general approaches, direct deprotonation or metallation by replacement of an α-substituent. Direct deprotonation of simple alkylboronic esters like 2,4,4,5,5-pentamethyl-1,3,2-dioxaborolane [**96** with $(RO)_2 = OCMe_2CMe_2O$, Equation 40 in Figure 1.26] is not possible even with strong bases like LDA or lithium 2,2,6,6-tetramethylpiperidide (LiTMP) [280]. An activating group must be present next to the boronate; a phenyl [280], thioether [313], trimethylsilyl [278, 314], triphenylphosphonium [314], or another boronate group [280] are all suitable in this role (i.e., **97–100**, Equation 40). Relatively hindered bases and a large boronic ester are preferable to favor C–H abstraction over

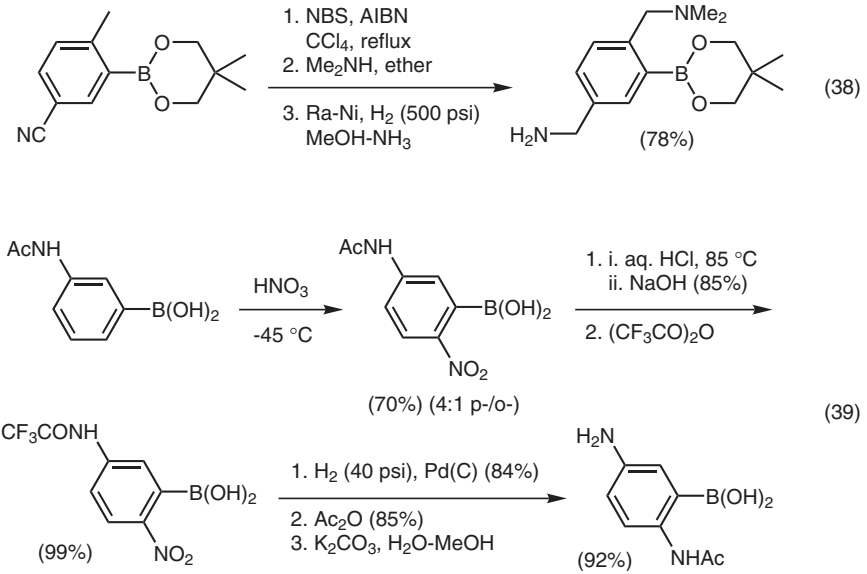


Figure 1.25 Chemoselective reduction reactions involving boronic acid derivatives.

the formation of a B–N ate adduct. For example, the carbanion of bis(1,3,2-dioxaborin-2-yl)methane [**100** with $(RO)_2 = O(CH_2)_3O$] can be generated by treatment with LiTMP (one equivalent) and one equivalent of the additive tetramethylethylenediamine (TMEDA) in tetrahydrofuran (–78 to 0 °C) [280]. Some of these species can be alkylated efficiently with primary halides and tosylates. Propanediol bisboronate **100** [$(RO)_2 = O(CH_2)_3O$] and the useful α-phenylthio derivative **101**, deprotonated with LDA, can even be alkylated twice in a sequential manner (Equation 41) [313]. The anion of **101** was also reacted with epoxides and lactones, and more recently it was used in the synthesis of functionalized boronic acid analogues of α-amino acids [315]. The carbanions of gem-diboronic esters **100** and trimethylsilylmethyl pinacolboronate [**99** with $(RO)_2 = OCMe_2CMe_2O$] undergo other transformations and also behave as substituted Wittig-like reagents by adding to aldehydes or ketones to provide alkenylboronates (e.g., entry 25, Table 1.4), which can also be oxidized and hydrolyzed to provide the homologated aldehydes [279, 316]. One drawback to the use of **100** is its preparation, which provides a low chemical yield. The corresponding carbanion can also be accessed by reaction of tris(dialkoxyboryl)methanes with an alkyllithium, but this approach lacks generality [317]. bis(1,3,2-Dioxaborin-2-yl)methane [**100** with $(RO)_2 = O(CH_2)_3O$] is suggested to be slightly more acidic than triphenylmethane (pK_a 30.6 in DMSO) [280], which confirms the rather weak stabilizing effect of a boronate group compared to a carboxyester (pK_a of dimethylmalonate ~13). Calculation of the Hückel delocalization energies confirmed that a boronate group is indeed slightly more stabilizing than a phenyl group (pK_a of diphenylmethane = 32.6 in DMSO), and the calculation of B–C π-bond orders indicated a very high degree of

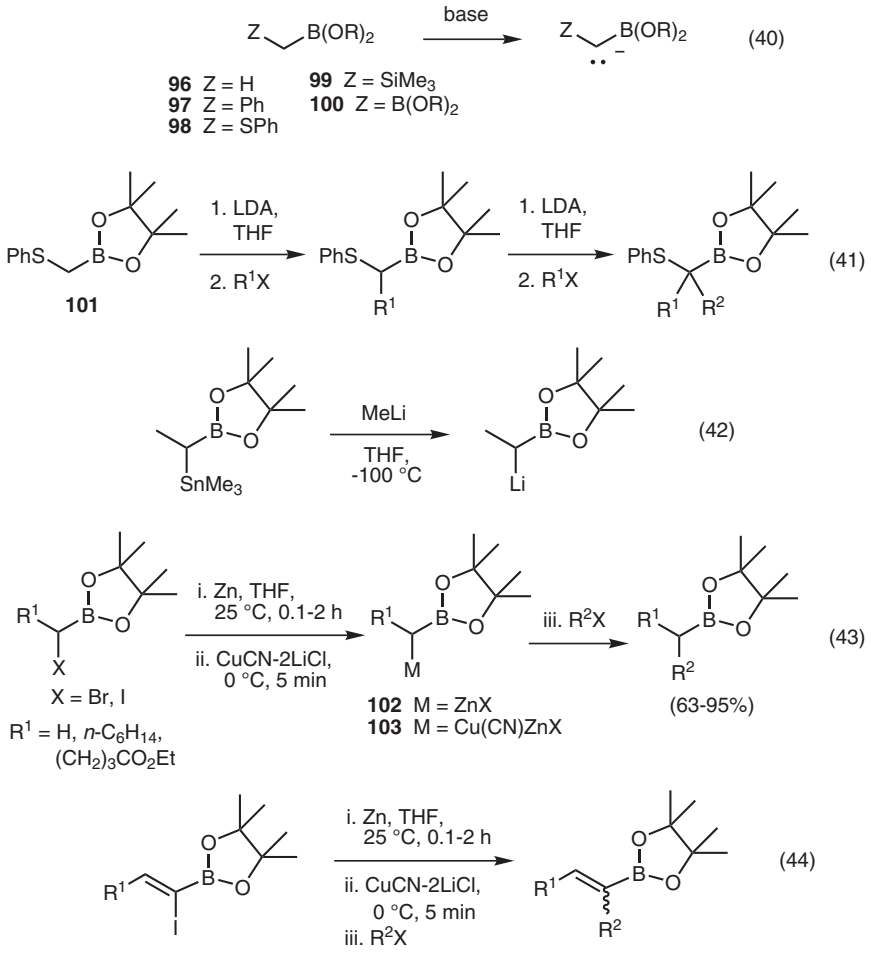


Figure 1.26 Formation and reactions of boronyl-substituted carbanions.

B–C conjugation in the carbanion [280]. This result appears to contradict the apparently modest degree of B–C π-overlap in alkenyl and aryl boronates discussed in Section 1.2.2.1; however, the latter cases concerned neutral species.

Other methods for the generation of α-boronyl carbanions include examples such as the lithiation of an α-trimethylstannyl derivative (Equation 42, Figure 1.26) [318], and the formation of the corresponding organozinc or organocopper species from α-bromo or α-iodo alkylboronates (Equation 43) [319]. In the latter cases, as demonstrated by Knochel, the mildness of the zinc and copper organometallic intermediates expands the range of compatible functional groups compared to the corresponding organolithium intermediates described above. Thus, reagents **102** and **103**, even with a carboxyester-containing side chain as R^1 substituent, were reacted with various electrophiles such as allylic halides, aldehydes, and Michael acceptors in good to excellent

yields (Equation 43). Likewise, the related sp^2 1,1-bimetallics can be generated from 1-iodoalkenylboronic pinacol esters, albeit with loss of stereochemical integrity of the olefin geometry (Equation 44) [320]. In one example, the Negishi coupling of a 1-iodozincalkenylboronate with an alkenyl iodide partner led to the formation of a 2-boronylbutadiene.

1.3.8.4 Reactions of (α-Haloalkyl)boronic Esters

One of the most powerful methods for modifying alkylboronic esters involves the nucleophilic attack and 1,2-rearrangement on (α-haloalkyl)boronic esters (**104**) (Figure 1.27). The addition of organometallic species to these boronic esters induces a facile boron-promoted displacement (Equation 45). Heteroatom-containing nucleophiles as well as organometallic reagents can be employed in this substitution reaction. Conversely, the addition of α-haloakyl carbanions to alkyl- and alkenylboronic esters leads to the same type of intermediates, and constitutes a formal one-carbon homologation of boronic esters (Equation 46). Sulfides from the addition of carbanions of α-thioethers can also undergo this rearrangement in the presence of mercuric salts [321]. A very efficient asymmetric variant of this chemistry was developed to allow the synthesis of chiral α-chloroalkylboronates, which can further undergo substitution reactions with a broad range of nucleophiles [322]. These α-chloroboronates are obtained in a very high enantiomeric purity through the Matteson asymmetric homologation reaction, which features the $ZnCl_2$-promoted addition of dichloromethyllithium to the boronates of pinanediol and a number of C2-symmetrical 1,2-diols. This elegant methodology was used in the synthesis of complex natural products, and is a cornerstone in the design and preparation of α-acylaminoboronic acid enzyme inhibitors.

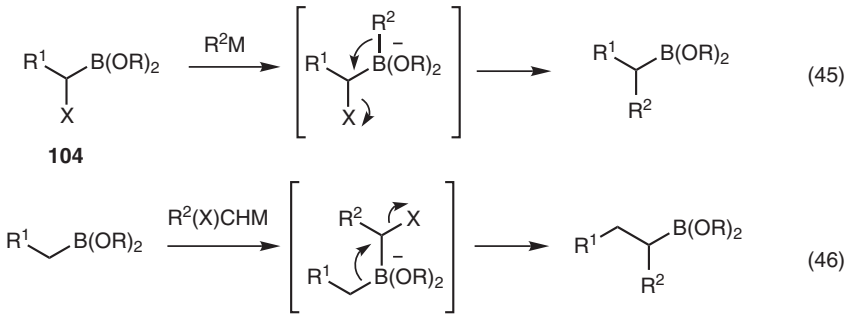
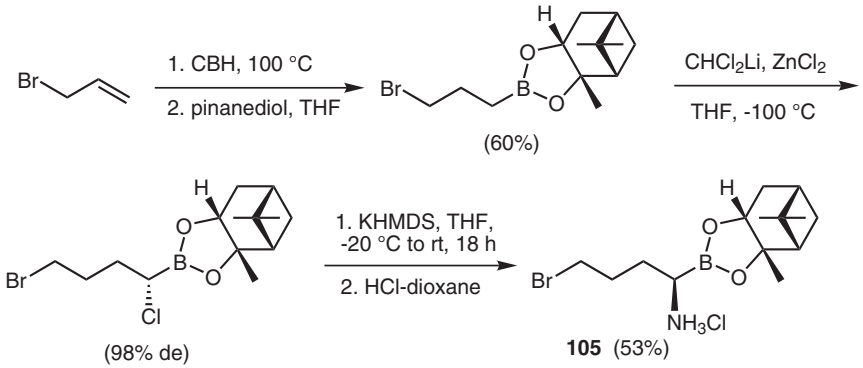


Figure 1.27 Substitution reactions of (α-haloalkyl)boronic esters.

As exemplified with the synthesis of **105** (Scheme 1.2), the latter compounds are obtained via the displacement α-chloroalkylboronates with the hexamethyldisilazide anion. This example also emphasizes the powerful neighboring group effect of boron, which allows selectivity in the addition of Cl_2CHLi in the presence of a primary alkyl bromide [323]. Other applications of (α-haloalkyl)boronates in stereoselective synthesis are detailed in Chapter 8.



Scheme 1.2 Application of the Matteson asymmetric homologation to the synthesis of chiral α-aminoboronic esters.

1.3.8.5 **Other Transformations**

Several other reactions can be performed on free boronic acids and the corresponding esters. Nitration of free arylboronic acids under fuming nitric acid and concentrated sulfuric acid has been known since the 1930s [324], albeit the use of low temperatures (e.g., Equation 39, Figure 1.25) is recommended in order to minimize protodeboronation (Section 1.2.2.5.3) [312, 325]. Other successful transformations of arylboronic acids include diazotization/hydrolysis [177], bromination [8], and nucleophilic aromatic substitutions [177]. Some alkenylboronates can be isomerized to allylboronates in high yields under Ru or Ir catalysis [326]. Schrock carbene formation is compatible with arylboronates [83], and radical additions to allyl or vinylboronates provide usefully functionalized alkylboronic esters [327]. Pinacol alkenylboronates are robust enough to tolerate a number of transformations, such as ester hydrolysis and a Curtius rearrangement (Equation 47, Figure 1.28) [328]. The scope of compatible transformations can be further increased with the help of a bulky boronate ester to effectively protect the susceptible boron center in oxidations, reductions, and other reactions (e.g. Scheme 1.3) [107]. Chapter 9 describes more addition and cycloaddition chemistry of alkenylboronic acid derivatives, including radical additions, cyclopropanation, and [4+2] cycloadditions.

Alkylboronic esters can also tolerate a wide range of conditions, and problems, if any, are usually encountered in the purifications steps rather than with the actual chemistry. The synthesis of 2-amino-3-boronopropionic acid, the boronic acid analogue of aspartic acid (**106**, Scheme 1.4), which included reactions such as carbethoxyester hydrolysis, a Curtius rearrangement, and hydrogenolysis, convincingly illustrates the range of possibilities [329]. Unlike the α-aminoalkylboronic acids described above, homologous compound **106** is stable and is thought to exist as an internal chelate or a chelated dimer in aqueous solutions. Lithiations in the presence of a boronic acid or the corresponding ester are difficult due to the electrophilic properties of the boron atom [330]. In this regard, protection of the boronyl group as a diethanolamine ester allowed the synthesis of *para*- and *meta*-chlorosulfonyl aryl-

boronic acids via a clean bromine/lithium exchange followed by trapping with sulfur dioxide (Equation 48, Figure 1.28) [331].

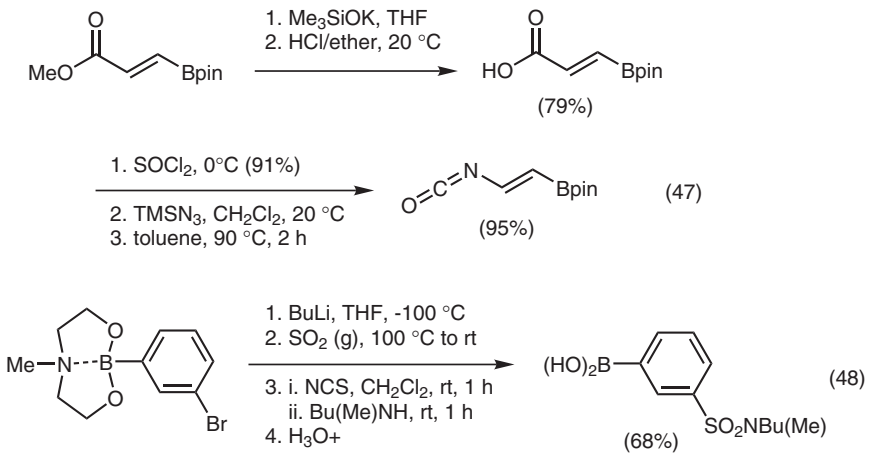
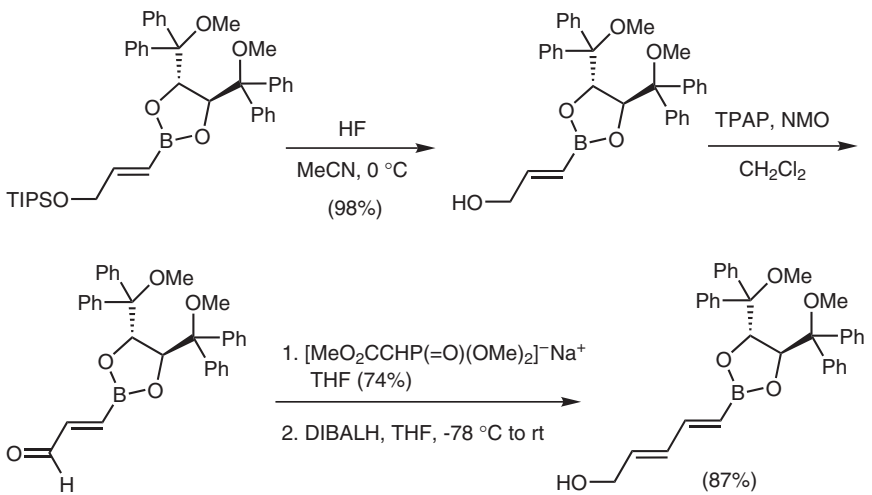
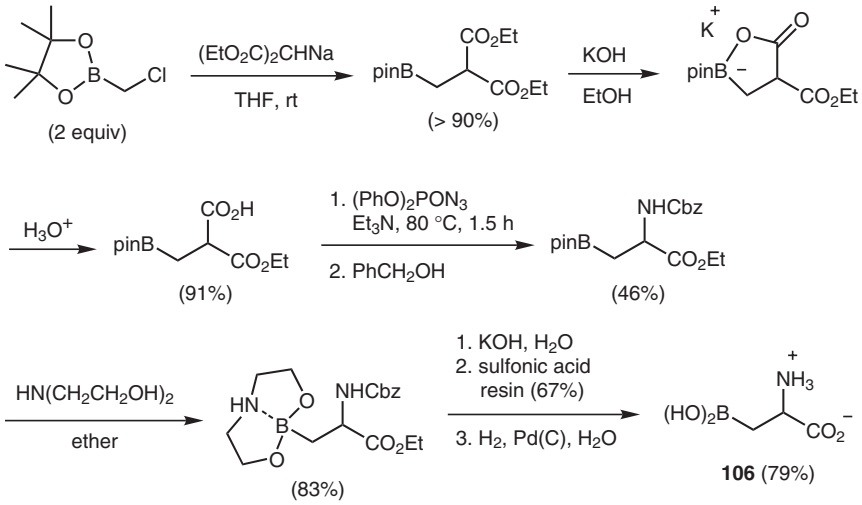


Figure 1.28 Other chemoselective reactions involving boronic acid derivatives.



Scheme 1.3 Sequence of transformations on a boronate-protected alkenylboronic acid.



Scheme 1.4 Synthesis of the boronic acid analogue of aspartic acid (**106**).

1.4
Isolation and Characterization

As discussed in Section 1.2.2.2, the polar and often amphiphilic character of boronic acids tends to make their isolation and purification difficult. In some cases, nonpolar organic solvents may be used to precipitate small boronic acids dissolved in a polar organic solvent. At higher pH where the hydroxyboronate species predominates (Section 1.2.2.4.1), however, boronic acids may be entirely miscible in water. For this reason, when extracting boronic acids from aqueous solutions, it is desirable to adjust the pH of the water phase to neutral or slightly acidic, and to use a polar organic solvent for an efficient partition. In addition to these potential difficulties in isolating boronic acids, their tendency to form oligomeric anhydrides further complicates characterization efforts. To palliate to these problems, boronic acids are often purified and characterized as esters. The following section provides a summary of useful methods and generalizations for the isolation and characterization of boronic acids and boronic esters.

1.4.1
Chromatography and Recrystallization

Most boronic acids can be recrystallized with ease. The choice of recrystallization solvent, however, greatly affects the relative proportions of free boronic acid and its corresponding anhydrides in the purified solid. Santucci and Gilman found that acids are usually obtained from aqueous solutions (i.e. water or aqueous ethanol), and anhydrides predominate when non-polar recrystallization solvents like ethylene dichlo-

ride are employed [332]. Recrystallization in benzene gives some dehydration, but to a lesser extent. Several other solvents have been used for the recrystallization of arylboronic acids. Much like carboxylic acids, most boronic acids interact strongly with silica gel. Depending on the degree of hydrophobicity of the boron substituent, chromatography and TLC on silica gel may be possible despite the high retentivity of boronic acids. A highly lipophilic trienylboronic acid was conveniently purified by silica gel chromatography [226]. Some polar boronic acids literally stick to silica and can hardly be eluted, even with eluents containing methanol or a small proportion of acetic acid. In other cases, filtration through a short plug of silica using acetone as coeluent [333], or the use of a polar eluent mixture of CH_2Cl_2 and EtOAc, were found suitable [325].

1.4.2
Solid Supports for Boronic Acid Immobilization and Purification

Recently, the increasing popularity of boronic acids as synthetic intermediates has motivated the development of solid supports and linkers to allow their immobilization and facilitate purification operations or derivatization (Figure 1.29). The appeal of these methods is particularly apparent in view of the difficulties often encountered in isolating pure boronic acids from both aqueous and organic solvent systems.

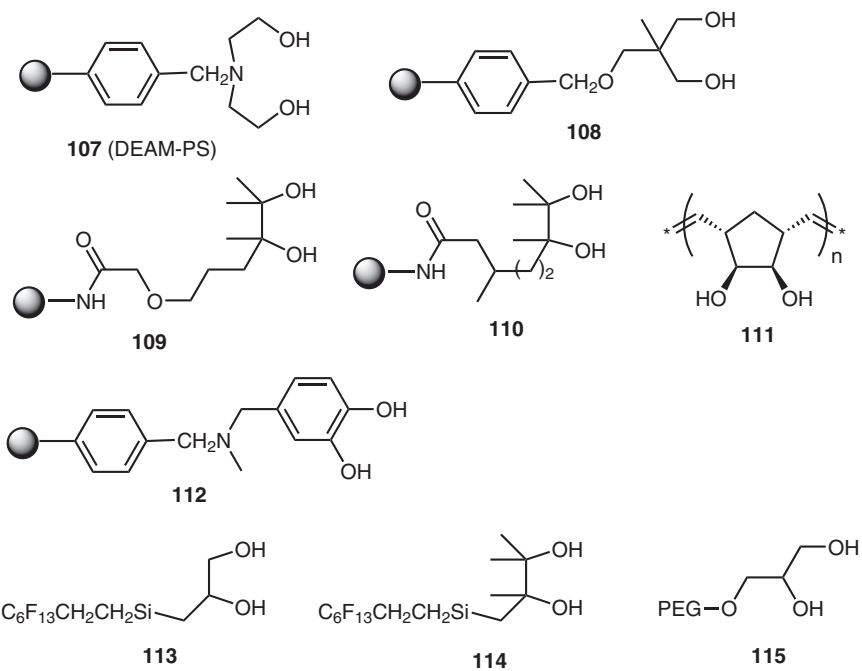


Figure 1.29 Diol-based supports for boronic acid immobilization and purification.

1.4.2.1 Diethanolaminomethyl Polystyrene

Diol-based insoluble polystyrene resins that can form supported boronate esters are obvious choices for immobilizing boronic acids. Hall and co-workers reported the first such example of solid support for boronic acids, the diethanolaminomethyl polystyrene resin (DEAM-PS, **107** in Figure 1.29) [334, 335]. The immobilization of alkyl, alkenyl, and arylboronic acids with this resin is straightforward, consisting simply of mixing a slight excess of DEAM-PS, as a suspension, in an anhydrous solution containing the boronic acid [334a]. Tetrahydrofuran is the solvent of choice as it dissolves most boronic acids. Notably, no azeotropic removal of the water released is needed, which is a benefit of B–N coordination in the resulting boronate adducts and of the highly hydrophobic nature of this polystyrene support. This simple procedure can be employed to scavenge or purify boronic acids from crude mixtures (Equation 49, Figure 1.30). Following resin washings, the desired boronic acid can be recovered upon treatment of the resin with a 5–10% solution of water in THF. A wide variety of arylboronic acids were immobilized with the DEAM-PS resin, and it has even been employed successfully in the derivatization of functionalized boronic acids [335]. Thus, amino-substituted arylboronic acids supported onto DEAM-PS were transformed into anilides and ureas, bromomethyl-substituted ones were reacted with amines, formyl-substituted ones were subjected to reductive amination with aldehydes, and carboxy-substituted phenylboronic acids were transformed into amides [335]. All these transformations afforded new arylboronic acid derivatives in very high purity directly after cleavage from the resin. The advantages of this solid-supported approach in avoiding the usual partitions between aqueous-organic solvent mixtures are best illustrated in the preparation of the BNCT candidate **118** (Equation 50, Figure 1.30), an amphoteric boronic acid soluble in aqueous solutions over the entire pH range (at pH > 8, the hydroxyboronate species is predominant, and at lower pH the amine is protonated). After immobilization of *p*-carboxyphenylboronic acid onto DEAM-PS to afford **116**, amide coupling with *N,N*-diethylethylenediamine followed by simple resin washings afforded the supported product **117**, which was released from the support to give **118** in very good yield and high purity (Equation 50) [335]. DEAM-PS supported boronic acids were also employed in the interesting concept of resin-to-resin transfer reactions (RRTR), whereby a phase transfer agent is used in situ to allow the transfer of one supported substrate to another resin-supported substrate. This convergent solid-phase synthetic strategy was applied to the Suzuki cross-coupling [336] and the borono-Mannich reactions [337]. These strategies are yet another benefit of the ease of boronic acid immobilization and cleavage when using DEAM-PS, which constitutes a significant advantage of this commercially available resin compared to most other diol-based resins described below.

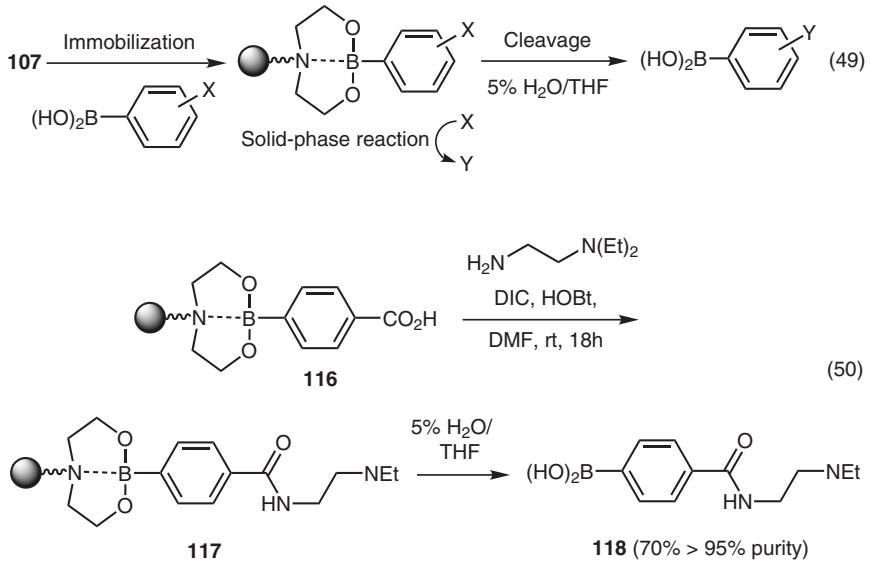


Figure 1.30 Solid-phase immobilization and derivatization of boronic acids using *N*,*N*-diethanolaminomethyl polystyrene (DEAM-PS, **107**).

1.4.2.2 **Other Solid-supported Diol Resins**

A macroporous polystyrene resin functionalized with a 1,3-diol unit, **108**, has been described by Carboni and co-workers [338]. Although the immobilization and subsequent cleavage of boronic acids both require harsher conditions than DEAM-PS, this support has also proven useful in the derivatization of functionalized boronic acids, as well as in several elegant C–C bond forming/release procedures [339] and a traceless cleavage of arenes [340]. Analogous pinacol-like linkers **109** and **110** were also described, although pre-attachment of the boronic acid prior to immobilization was required in these examples [341, 342]. The use of a ROMPgel diol (**111**) in the immobilization of allylboronates was reported to simplify the purification of the homoallylic alcohol products resulting from aldehyde additions [343]. More recently, a catechol resin (**112**) was found to be effective in the immobilization and derivatization of functionalized arylboronic acids [344].

1.4.2.3 **Soluble Diol Approaches**

Fluorous phase purification methodologies using fluoroalkyl-tagged substrates combine the advantages of homogenous reaction conditions of solution-phase reactions with the ease of purification of solid-phase methods. In this regard, a new class of pinacol-like and other diol-based polyfluoroalkyl linkers such as **113** and **114** were described [345]. The resulting fluorous boronates were employed in various transformations, and allowed a facile purification by simple partition between fluorous and organic solvents. A dendritic high-loading polyglycerol, **115**, was shown to be effec-

tive in immobilizing arylboronic acids and in facilitating the purification of biaryl products from homogeneous Suzuki cross-coupling reactions [346].

1.4.3 Analytical and Spectroscopic Methods for Boronic Acid Derivatives

1.4.3.1 Melting Points and Combustion Analysis

The difficulty in measuring accurate and reproducible melting points for free boronic acids has long been recognized [347]. Rather than true melting points, these measurements are often more reflective of dehydration or decomposition points [185, 348]. The lack of reproducibility for a given boronic acid may originate from the water contents of the sample used, which affects the acid–anhydride transition. Moreover, as mentioned above, the water content also depends on the recrystallization solvent [332]. For these reasons, it is often more appropriate to report melting points of boronic acids as their diethanolamine ester (Section 1.2.3.2.1). Likewise, combustion analysis of free boronic acids may provide inaccurate results depending on the recrystallization method employed.

1.4.3.2 Mass Spectrometry

One useful diagnostic information in the mass spectrometric analysis of boronic acid derivatives is the observation of boron's isotopic pattern, which is constituted of ^{10}B (20% distribution) and ^{11}B (80%). However, unless other functionalities help increase the sensitivity of a boronic acid containing compound, it is often difficult to obtain intense signals with most ionization methods due to the low volatility of these compounds. This problem is exacerbated by the facile occurrence of gas-phase dehydration and anhydride (boroxine) formation in the ion source. To minimize these thermal reactions and improve volatility, cyclic boronates such as the 1,2-ethanediol, 1,3-propanediol, and pinacol esters are employed. These derivatives were even made on an analytical scale [349]. Fragmentation patterns of various para-substituted arylboronic esters of 1,2-ethanediol were studied using electron impact ionization and several deboronative fragmentation pathways were observed [350]. The nature of the para substituent was found to have a marked influence. In another study by GC-MS, ortho substituents were found to interact strongly during fragmentation [349]. Boropeptides, a popular class of enzyme inhibitors (Section 1.6.5), and phenylboronic acid were characterized by positive-ion ammonia chemical ionization with different diols as bench-top derivatization agents [351].

1.4.3.3 Nuclear Magnetic Resonance Spectroscopy

Boron compounds, including boronic acid derivatives, can be conveniently analyzed by NMR spectroscopy [352]. Of the two isotopes, ^{11}B is the most abundant (80%) and possesses properties that are more attractive towards NMR. These attributes include its lower resonance frequency, spin state (3/2) and its quadrupole moment, a wide range of chemical shifts, and its higher magnetic receptivity (16% of ^{1}H). When analyzing boronic acids in non-hydroxylic solvents by NMR spectroscopy, it is often necessary to add a small amount of deuterated water (e.g. one or two drops) to the sam-

ple in order to break up the oligomeric anhydrides. Alternatively, analysis in anhydrous alcoholic solvents such as methanol will allow detection of the in situ formed methanolic ester. Observation of the ^{11}B nucleus against a reference compound (e.g. BF_3) is straightforward with modern instruments, and can be especially revealing of the electronic characteristics [33] and coordination state of the boronate moiety. The boron resonance of free boronic acids and tricoordinate ester derivatives is generally detected in the 25–35 ppm range, and tetracoordinate derivatives such as diethanolamine esters resonate at around 10 ppm [353]. In ^{13}C analysis, carbons next to the ^{11}B atom tend to be broadened – often beyond detection limits. Consequently, with aromatic boronic acids the signal of the quaternary carbon bearing the boron atom, which is already depleted by a long relaxation time, is very difficult to observe over the background noise.

1.4.3.4 Other Spectroscopic Methods

Despite their limited structure determination capabilities, ultraviolet and infrared spectroscopy were determinant characterization techniques in the early days of boronic acid research [332]. Notable IR absorptions are the strong H-bonded OH stretch (3300–3200 cm^{-1}), and a very strong band attributed to B–O stretch (1380–1310 cm^{-1}). IR is particularly diagnostic of the presence of boronic anhydrides. Upon anhydride (boroxine) formation, the OH stretch disappears and a new strong absorption appears at 680–705 cm^{-1} [68].

1.5 Overview of the Reactions of Boronic Acid Derivatives

1.5.1 Metallation and Metal-catalyzed Protodeboronation

In 1882, Michaelis and Becker described the preparation of phenylmercuric chloride (**119**) from the reaction of phenylboronic acid and aqueous mercuric chloride (Equation 51, Figure 1.31) [198b]. Benzylboronic acid was transformed into benzylmercuric chloride in the same manner, and both compounds were found to resist hydrolysis under the conditions of their preparation. Mechanistic studies later showed that this reaction proceeds through the hydroxyboronate ion [354]. Catechol and pinacol alkenylboronic esters can also be easily transformed into the corresponding organomercurial derivative with retention of configuration (Equation 52) [355, 356]. One of the early realizations concerning the reactivity of arylboronic acids was that several metal ions [other than Hg(II)] can induce protodeboronation in water, presumably via the intermediacy of an arylmetal species (Equation 51). Thus, Ainley and Challenger found that hot solutions of copper sulfate, cadmium bromide, and zinc chloride produce benzene [324]. As phenylboronic acid is stable to dilute hydrochloric acid, it was deduced that the deboronation occurred through the formation of intermediates similar to **119** (Figure 1.31) and their reaction with water, and not from the possible release of acid by hydrolysis of the metal salt. Instead of giving benzene,

cupric chloride and bromide were found to provide the respective phenyl chloride and bromide [324]. Halide salts of beryllium, magnesium, and calcium did not react with phenylboronic acid [324]. Arylboronic acids were transformed into arylthallium derivatives in similar fashion [357], and alkylboronic acids were unreactive under the same conditions [78]. Ammonical solutions of silver nitrate also induce protodeboronation of arylboronic acids, with production of silver oxide [176]. Aliphatic boronic acids behave differently and tend, rather, to undergo a reductive coupling to give dimeric alkane products [76]. Kuivila and co-workers studied the mechanism of metal ion catalysis in the aqueous protodeboronation of arylboronic acids [358]. Substituent effects and the influence of pH were investigated, and both base and cadmium catalysis pathways were evidenced for this reaction. The order of effectiveness of the different metal ions at effecting aqueous deboronation was established as Cu(II) > Pb(II) > Ag(I) > Cd(II) > Zn(II) > Co(II) > Mg(II) > Ni(II).

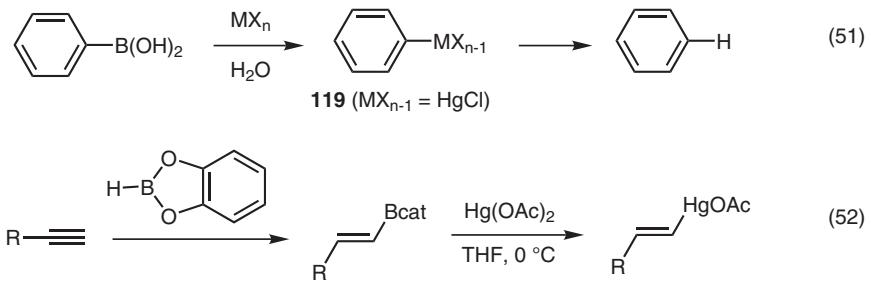


Figure 1.31 Transmetallation-protodeboronation of boronic acids.

From a synthetic chemistry standpoint, reaction of the metallated intermediates with electrophiles other than a proton is more attractive. Indeed, one of the most important recent developments in boronic acid chemistry strove from the discoveries that transition metals such as palladium(0), rhodium(I), and copper(I) can oxidatively insert into the B–C bond and undergo further chemistry with organic substrates. These processes are discussed in Sections 1.5.3 and 1.5.4.

1.5.2 Oxidative Replacement of Boron

1.5.2.1 Oxygenation

The treatment of arylboronic acids and esters with alkaline hydrogen peroxide to produce the corresponding phenols was first reported more than 75 years ago [324]. The oxidation of alkyl- and alkenyl- boronic acid derivatives leads to alkanols [40] and aldehydes/ketones, respectively [85, 257, 279, 316]. With α-chiral alkylboronates, the reaction proceeds by retention of configuration (Equation 53, Figure 1.32) [359, 121]. In fact, the oxidation of boronic acids and esters is a synthetically useful process, mainly in the preparation of chiral aliphatic alcohols via asymmetric hydroboration reactions [300, 302], or from Matteson homologation chemistry [322]. Paradoxically, the

oxidation of arylboronic acids is not a popular and economical approach for preparing phenols. It was recently reported, however, that a one-pot C–H activation/borylation/oxidation sequence gives access to meta-substituted phenols that would be difficult to obtain by other means (Equation 54) [360]. The mechanism of the aqueous basic oxidation of phenylboronic acid was investigated by Kuivila [361]. The rate is first order each in boronic acid and hydroperoxide ion, which led the authors to propose the mechanism of Equation 55 (Figure 1.32). The transition state features a boron-to-oxygen migration of the ipso carbon. Milder oxidants, such as anhydrous trimethylamine *N*-oxide [362], oxone [363], and sodium perborate [364, 365], can also be employed for the oxidation of most types of boronic acid derivatives. Notably, perborate was reported to give a cleaner oxidation of alkenylboronic acids into aldehydes compared to hydrogen peroxide [316]. Interestingly, the combined use of diacetoxyiodobenzene and sodium iodide under anhydrous conditions transforms

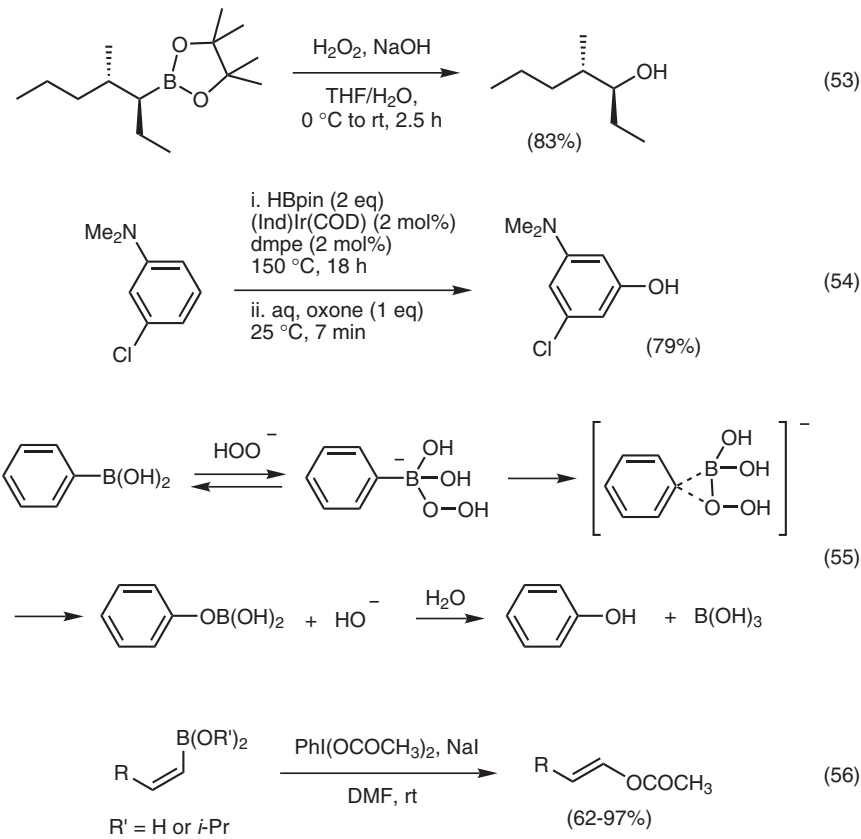


Figure 1.32 Oxidation of boronic acids (esters).

alkenylboronic acids and esters into enol acetates in a stereospecific manner (Equation 56) [366].

1.5.2.2 Amination

Aryl azides can be accessed indirectly from arylboronic acids via in situ generated aryllead intermediates (Equation 57, Figure 1.33) [367]. A mild procedure for ipso-nitration of arylboronic acids was recently developed (Equation 58), and a mechanism proposed [368]. The common methods and reagents for electrophilic amination, however, do not affect boronic acids and their esters. These processes require the intermediacy of more electrophilic boron substrates such as borinic acids or dichloroboranes. For example, enantiomerically pure propanediol boronates, which are accessible from the asymmetric hydroboration of alkenes with Ipc_2BH followed by acetaldehyde-promoted workup and transesterification, can be treated sequentially with MeLi and acetyl chloride. The resulting borinic ester is sufficiently electrophilic to react at room temperature with the amination reagent hydroxylamine-O-sulfonic acid with retention of stereochemistry to give primary amines in essentially 100% optical purity (Equation 59) [369]. The preparation of optically pure secondary amines from alkyl azides requires the intermediacy of the highly electrophilic dichloroboranes (Equation 60) [163], which can be made from boronic esters or monoalkylboranes as described in Section 1.2.3.6. A convenient one-pot procedure was described

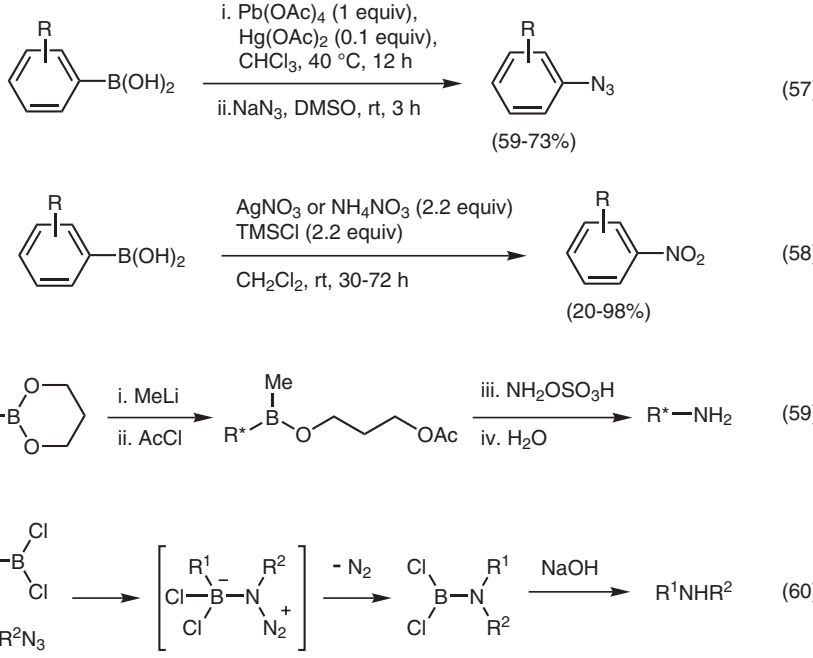


Figure 1.33 Oxidative amination of boronic acid derivatives.

with bis(isopropylamino)borane substrates, which can generate the corresponding dichloroboranes in situ by treatment with dry HCl [370]. Intramolecular variants of the reaction with alkylazides give access to pyrrolidines and piperidines [371].

1.5.2.3 **Halogenation**

1.5.2.3.1 Arylboronic Acids and Esters

As described above, cuprous chloride and bromide provide the corresponding ipso-substituted phenyl halides from benzeneboronic acid [324]. Likewise, arylboronic acids are halodeboronated regioselectively by the action of aqueous chlorine, bromine, and aqueous iodine containing potassium iodide [324]. Alkylboronic acids do not react under the same conditions [40]. Kuivila and co-workers have studied the kinetics of brominolysis in aqueous acetic acid and found that bases catalyze the reaction [372]. This observation and a Hammett plot of ten arylboronic acids [373] are consistent with a proposed electrophilic ipso-substitution mechanism involving the usual weakening effect of the C–B bond through formation of a boronate anion (Equation 61, Figure 1.34). *N*-Bromo- and *N*-iodosuccinimides convert arylboronic acids into the corresponding aryl halides in good to excellent yields [374]. Most arylboronic acids react in refluxing acetonitrile whereas the most activated ones such as 2-methoxyphenylboronic acid are iodinated at room temperature. Boronic esters provide significantly lower yields, and *N*-chlorosuccinimide is essentially unreactive, even in the presence of bases. Recently, the use of 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) under catalysis by sodium methoxide was shown to be an efficient bromodeboronation method for arylboronic acids when acetonitrile is used as solvent (Equation 62, Figure 1.34) [375]. The corresponding reagent DCDMH leads to the isolation of aryl chlo-

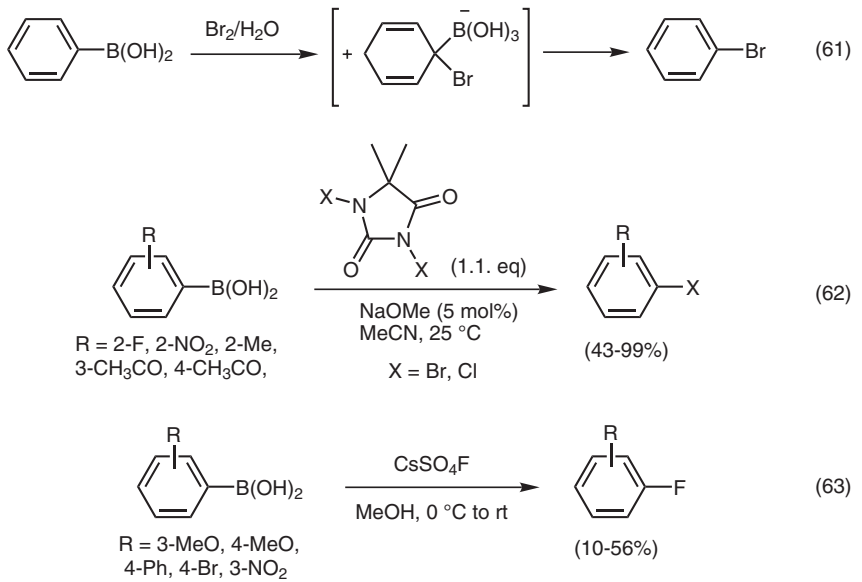


Figure 1.34 Halogenation of arylboronic acids.

rides. Aryl fluorides can be obtained in rather modest yield by treatment of arylboronic acids with cesium fluoroxysulfate ($CsSO_4F$) in methanol (Equation 63) [376]. Aryl(phenyl)iodonium salts are formed by treatment of arylboronic acids with trifluoromethanesulfonic acid and diacetoxyiodobenzene in dichloromethane [377].

1.5.2.3.2 Alkenylboronic Acids and Esters

The sequential treatment of alkenylboronic esters with bromine in ethereal anhydrous solvent, then with sodium hydroxide or alkoxides in a one-pot fashion, provides the corresponding alkenyl bromides with inversion of olefin geometry (Equations 64 and 65, Figure 1.35) [378–380]. A reasonable mechanism to account for the inversion is based on the formation of a vicinal dibromide followed by a trans bromodeboronation promoted by the addition of the base (Equation 64) [380]. The related iodinolysis process is complementary, giving alkenyl iodides with retention of olefin geometry (Equations 66 and 67) [381–383]. The procedure involves the simultaneous action of iodine and aqueous sodium hydroxide, and a tentative mechanism involving the syndeboronation of an iodohydrin intermediate has been proposed to explain the stere-

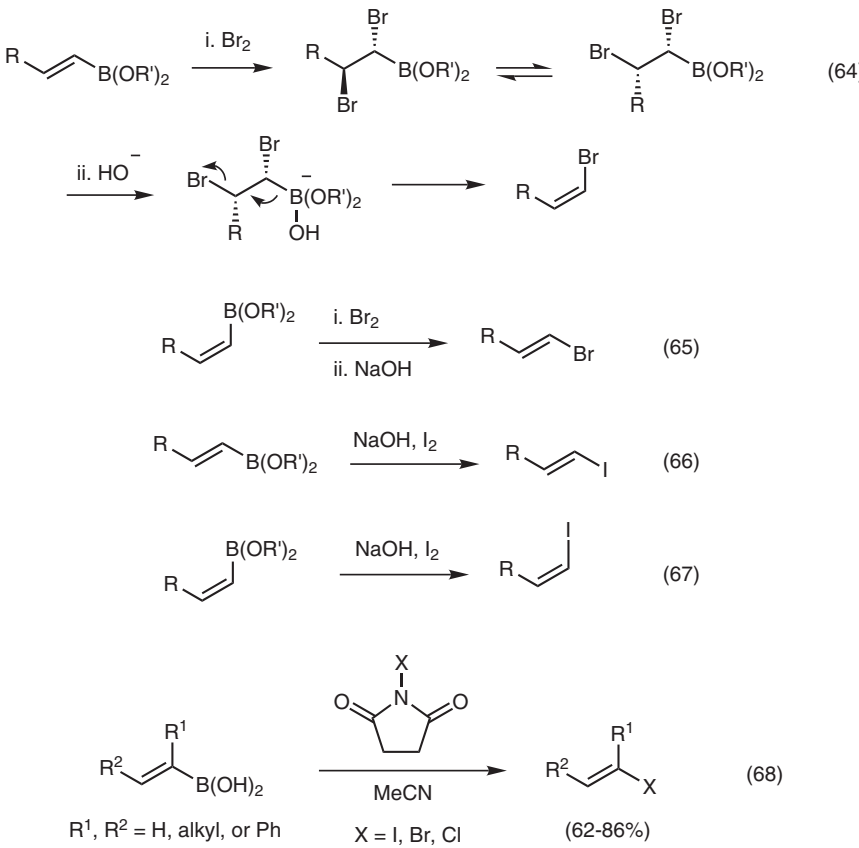


Figure 1.35 Halogenation of alkenylboronic acids (esters).

ochemistry of this reaction [380]. Like the bromination process, however, in most cases a sequential treatment of the alkenylboronic acid with iodine, then with sodium hydroxide, provides the corresponding alkenyl iodides by inversion of geometry [380]. In both cases, boronic acids can be used directly with only one equivalent of halogen, whereas boronic esters can be transformed effectively with at least two equivalents of the requisite halogen. The use of ICl and sodium acetate was also demonstrated [384]. Indeed, the combination of ICl and sodium methoxide as base was more efficient with hindered pinacol alkenylboronates, and both isomers can be obtained selectively from a single (*E*)-1-alkenylboronate, depending on the order of addition of the reagents [385]. A mechanism involving the boronate ion was invoked in this variant as well, and, notably, a pinacol alkylboronic ester failed to react. Petasis and Zavialov reported a mild halogenation procedure for various types of alkenylboronic acids using halosuccinimides as reagents (Equation 68, Figure 1.35) [386]. The reactions proceed in acetonitrile at room temperature to provide high yields of alkenyl halide products with retention of olefin geometry. The stereoselectivity was tentatively explained through a pseudo-intramolecular substitution mechanism within a tetracoordinate boron intermediate. The chlorination variant with *N*-chlorosuccinimide, however, requires the use of triethylamine as base. Alkenylboronic acids were also chlorinated with chlorine by inversion olefin geometry [387].

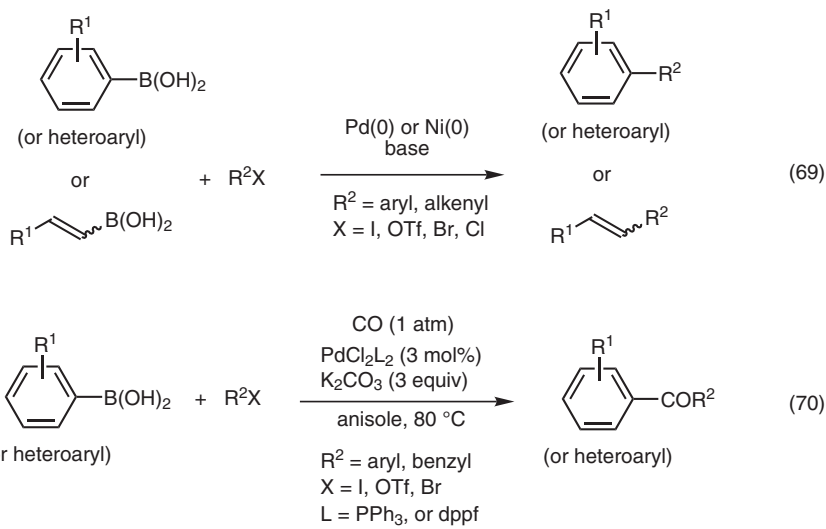


Figure 1.36 Transition metal-catalyzed coupling of boronic acids (esters) with carbon halides/triflates (Suzuki cross-coupling reaction).

1.5.3
Carbon–Carbon Bond forming Processes

1.5.3.1 Palladium-catalyzed Cross-coupling with Carbon Halides (Suzuki Coupling)

A 1979 *Chemical Communications* paper by Miyaura and Suzuki reported findings generally regarded as the most important discovery in the recent history of boronic acid chemistry [388]. This paper described a Pd(0)-catalyzed coupling between alkenyl boranes or catecholates and aryl halides, in the presence of a base, providing arylated alkene products in high yields. Soon thereafter, a seminal paper on the synthesis of biaryls by coupling of phenylboronic acid with aryl bromides and halides was reported (Equation 69, Figure 1.36) [389]. Since then, significant improvements have been made through an optimization of the different reaction parameters such as catalyst, ligands, base, solvent, and additives. These advances have been reviewed regularly [390].

The accepted mechanism for the aqueous basic variant involves oxidative addition of the halide substrate to give a Pd(II) intermediate, followed by a transmetallation, and a final reductive elimination that regenerates the catalyst (Figure 1.37) [391–393]. The two key catalytic intermediates have been observed by electrospray mass spectrometry [394]. Although the exact role and influence of the base remains unclear [395], the transmetallation is thought to be facilitated by base-mediated formation of the tetracoordinate boronate anion [396], which is more electrophilic than the free boronic acid (Sections 1.5.1 and 1.5.2). A useful carbonylative variant has also been developed to access benzophenones (Equation 70) [397], which can also be produced from the coupling of acid chlorides [398] or anhydrides [399]. A variant of this method allows the preparation of α,β-unsaturated esters from alkenylboronic esters [243]. In all of these reactions, one dreaded limitation with some ortho-substituted and electron-poor arylboronic acids is the possible occurrence of a competitive protolytic deboronation, which is exacerbated by the basic conditions and the use of a transition metal catalyst (Section 1.5.1). Methods to minimize this side reaction were developed; in particular the use of milder alternative bases [400] such as fluoride salts [401], and

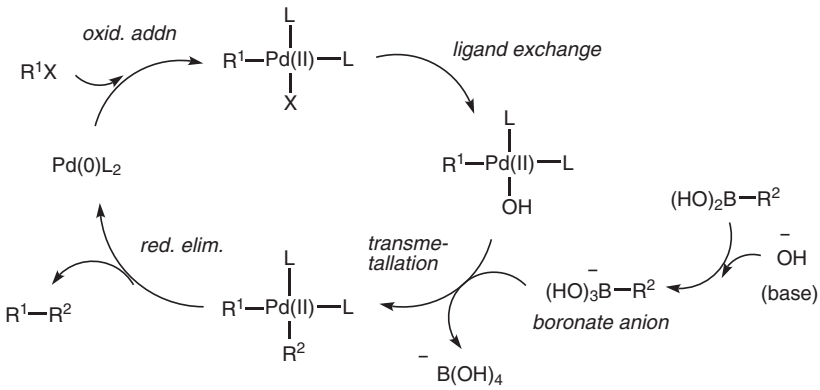


Figure 1.37 Accepted mechanism for the Suzuki cross-coupling reaction under aqueous conditions.

non-aqueous conditions [402]. Competitive homo-coupling of the arylboronic acid can also compete, but it can also be an attractive process for making symmetrical biaryls [403]. Despite these impediments, the venerable Suzuki–Miyaura cross-cou-

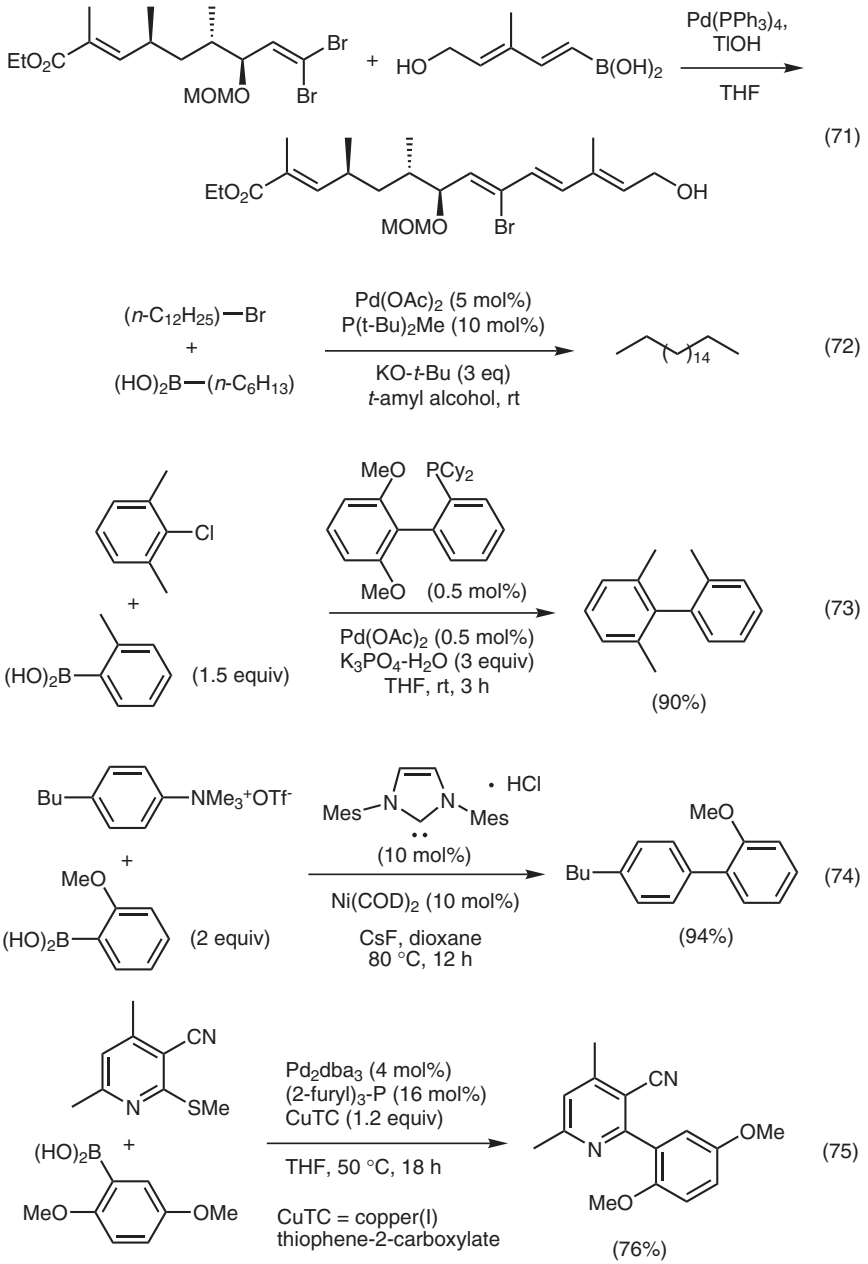


Figure 1.38 Selected examples of Suzuki-cross coupling reactions.

pling reaction has become the most versatile method to synthesize a broad range of biaryl compounds that find widespread uses as pharmaceutical drugs and materials. The reaction is particularly useful in combination with orthometallation approaches to generate the arylboronic acid substrate [404].

Alkenylboronic acids and esters are also very useful substrates (Equation 71, Figure 1.38) [405], in particular to access substituted olefins and dienyl moieties commonly encountered in several classes of bioactive natural products [282, 406]. To this end, Kishi and co-workers examined the influence of the base, and developed an optimal variant using thallium hydroxide [281]. Recently, allylic alcohols were found to couple directly with alkyl and alkenyl boronic acids without the aid of a base [407]. In rare cases, the Suzuki reaction has been applied to the use of alkylboronic acids [296, 408], including cyclopropylboronic acids [409]. Hitherto notorious for their tendency to undergo β-hydride elimination, alkyl bromides are now suitable as electrophiles under carefully optimized conditions that even allow Csp^3–Csp^3 couplings with alkylboronic acids (Equation 72) [410]. The Suzuki reaction has also been applied very successfully in solid-phase chemistry and combinatorial library synthesis [411]. It has been applied industrially [412], especially in medicinal chemistry, e.g. in the production of the antihypertensive drug losartan [195].

In the past few years alone, several new and further improved catalysts and ligands have been developed for difficult substrates such as aryl chlorides, which are cheaper and more available than bromides [413]. Amongst other advances, new phosphine-based systems developed by Fu [414], Buchwald [415], and others [416] even allow room-temperature couplings with aryl chlorides. For example, Buchwald and co-workers recently reported a universal palladium catalyst system, based on a rationally designed ligand with unprecedented stability and scope, for couplings of hindered aryl chlorides at room temperature (Equation 73, Figure 1.38) [417]. Phosphine free systems based on N-heterocyclic carbene ligands perform very well with hindered boronic acids and electrophiles [418]. Other transition metals catalyze the reaction, notably nickel [419] and ruthenium [420], albeit the range of suitable substrates seems more limited. Interestingly, advantageous ligand-free couplings [421] and even the surprising claim of palladium-free couplings have been reported [422]. Other classes of substrates such as aryltosylates [423] and arylammonium salts [424] (Equation 74) were recently uncovered to further expand the scope of this cross-coupling chemistry. Likewise, arylsulfonium salts [425], thioesters [426], and thioethers [427] are suitable electrophilic substrates. For example, heteroaromatic thioethers couple to arylboronic acids under base-free conditions promoted by copper(I) thiophene-2-carboxylate (Equation 75) [428]. More recent developments in the synthesis of biaryl products by the coupling of aromatic boronic acids with aromatic electrophiles are described in detail by Professor Suzuki in Chapter 3.

1.5.3.2 **Allylation of Carbonyl Compounds**

The addition of allylboronates to aldehydes was first discovered in 1974 [429]. This reaction has since found tremendous use in the stereoselective synthesis of acetate and propionate units embodied in numerous natural products (Equation 76, Figure 1.39) [430]. The tartrate-based chiral allylboronates, for example, have become one of the

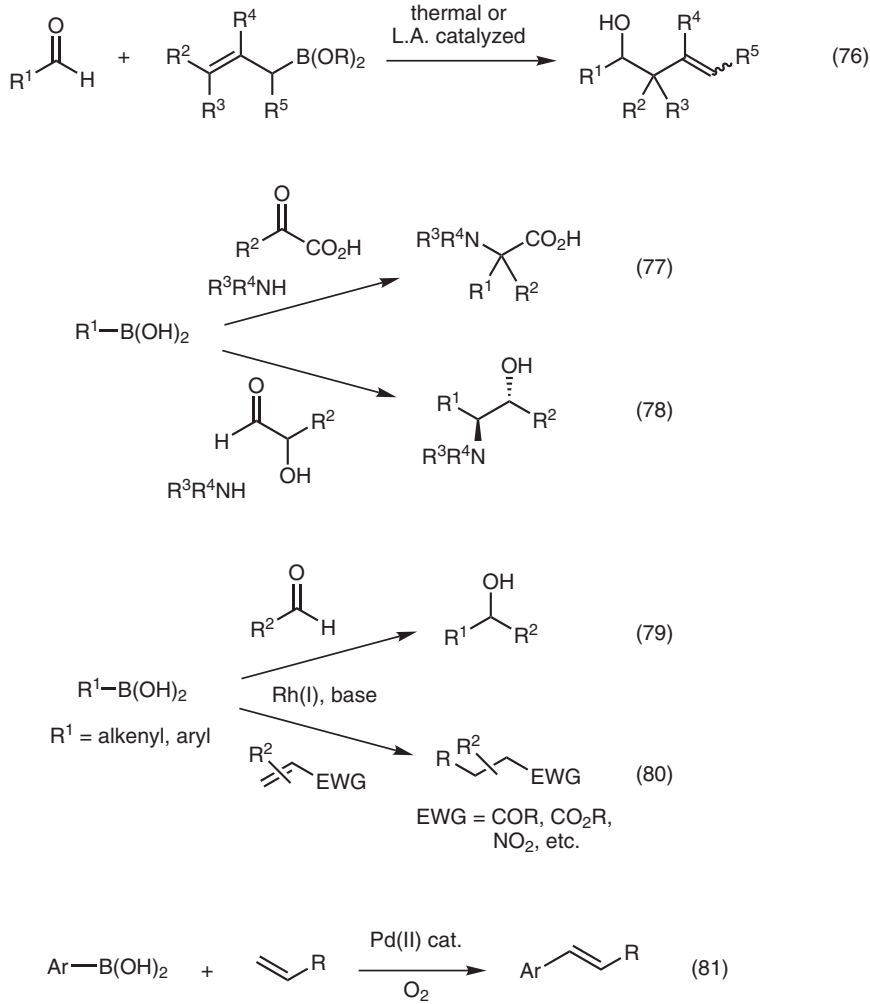


Figure 1.39 Other C–C bond forming reactions involving boronic acids (esters).

most recognized classes of chiral reagents in organic synthesis [102]. One of the most recent developments of this reaction is the discovery that additions of allylboronates to aldehydes can be catalyzed by Lewis acids [431]. The dramatic rate acceleration observed allows a substantial decrease of the reaction temperature, which in turn leads to outstanding levels of diastereo- and enantioselectivity with camphordiol-based reagents [432]. The preparation of allylboronates and their most recent synthetic applications are described in Chapter 6.

1.5.3.3 Uncatalyzed Additions to Imines and Iminiums

In 1997, Petasis and Zavialov described a novel uncatalyzed three-component reaction between α-ketoacids, amines and boronic acids, providing a novel synthetic route to α-amino acids (Equation 77, Figure 1.39) [433]. The use of α-hydroxyaldehydes lends access to β-aminoalcohols in high yields and excellent stereoselectivity (Equation 78) [434]. Both alkenyl and aryl boronic acids can be employed. This powerful new reaction process and variants thereof are described in Chapter 7.

1.5.3.4 Rhodium-catalyzed Additions to Aldehydes and Alkenes

Another recent breakthrough in organoboron chemistry is the exciting discovery that rhodium(I) complexes catalyze the addition of boronic acids to carbonyl compounds [435] and a wide range of alkene substrates (Equations 79 and 80, Figure 1.39) [436]. The latter process can even provide enantioselectivities over 99% in 1,4-additions to enones [437]. Very recently, cinnamaldehydes were found to give an anomalous self-conjugate reduction/cross-coupling tandem reaction [438], and arylboroxines reportedly undergo a catalytic asymmetric addition to *N*-tosylarylimines [439]. Palladium and nickel catalysts promote similar additions of boronic acids onto unactivated alkynes [440], allenes [441], and 1,3-butadienes [442]. These new reactions of boronic acids are reviewed in detail in Chapter 4.

1.5.3.5 Heck-type Coupling to Alkenes and Alkynes

Several reports have highlighted the ability of boronic acids to undergo rhodium- [443], ruthenium- [444], iridium- [445], or palladium-catalyzed [446] addition–dehydrogenation reactions on alkenes (Equation 81, Figure 1.39) [446c]. Similar couplings to terminal alkynes were reported [447].

1.5.4 Carbon–Heteroatom Bond forming Processes

1.5.4.1 Copper-catalyzed Coupling with Nucleophilic Oxygen and Nitrogen-containing Compounds

In 1998, groups led by Chan, Evans, and Lam independently reported their observations that copper diacetate promotes the coupling of aryl and heteroaryl boronic acids to moderately acidic heteroatom-containing functionalities like phenols, thiols, amines, amides, and various heterocycles (Equation 82, Figure 1.40) [448–450]. The potential of this mild and general method was convincingly exemplified with the syntheses of the diaryl ether units of a thyroxine intermediate (Equation 83) [449] and the teicoplanin aglycon related to vancomycin [184]. This new reaction has since been extended to other classes of substrates and, in particular, to applications in solid-phase synthesis [451]. A mechanism was suggested based on transmetallation of the boronic acid with $Cu(OAc)_2$ followed by ligand exchange with the nucleophilic substrate, and reductive elimination to give the coupling product [448]. This new reaction of boronic acids constitutes the main topic of Chapter 5.

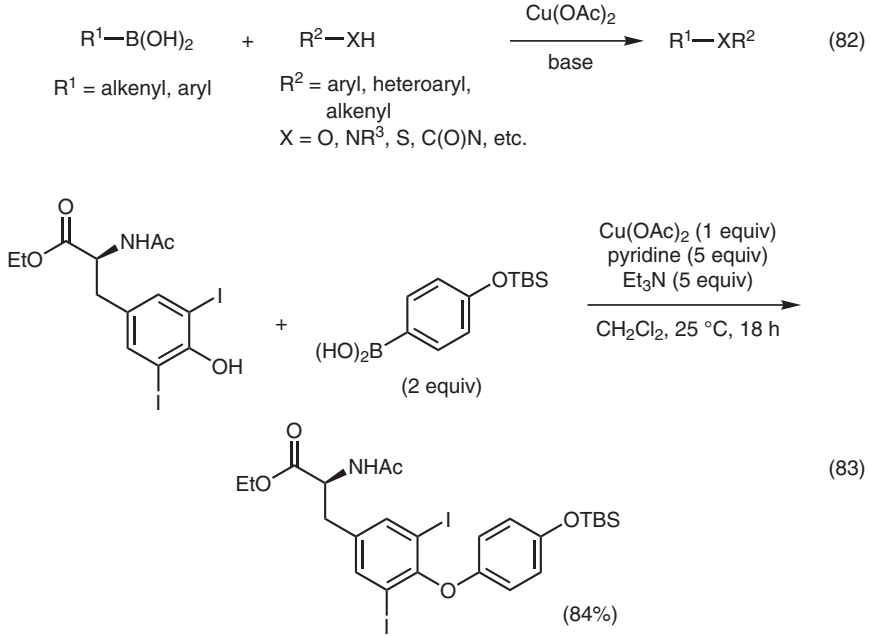


Figure 1.40 Copper-catalyzed coupling of boronic acids with nucleophilic oxygen and nitrogen-containing compounds.

1.5.5
Other Reactions

The B–C bond of alkynylboronic esters is labile enough to allow their uncatalyzed nucleophilic addition to enones, and an asymmetric variant has been developed using binaphthyl alkynylboronates (Equation 84, Figure 1.41) [452]. 1,3-Dicarbonyl compounds are arylated with arylboronic acids in the presence of lead tetraacetate and catalytic $Hg(OAc)_2$ under in situ conditions that promote a rapid boron–lead transmetallation (Equation 85) [453]. Allylic carbonates [454] and even amines [455] provide cross-coupling products with boronic acids under nickel catalysis. The metalation of *ortho*-bromobenzeneboronic esters was recently shown to be an effective route to benzyne complexes of Group 10 metals (e.g., Ni, Pd) [456]. Arylboronic acids have been employed as aryl source in enantioselective zinc-promoted additions to aldehydes [457]. Likewise, arylboronic esters were used in a ruthenium-catalyzed ortho-arylation of aromatic ketones via C–H activation/functionalization (Equation 86) [458], or in a dealkoxylation/functionalization [459]. Cyclobutanones undergo a C–C bond insertion/functionalization with arylboronic acids (Equation 87) [460]. Boronic acids have been employed in multicomponent reaction processes other than the Petasis reaction (Section 1.5.3.3). For example, they react with diazocyclopentadiene and a rhenium(I) tricarbonyl complex to give new monoalkylated cyclopentadienyl rhenium

complexes [461]. Jamison and co-workers reported a nickel-catalyzed three-component reaction between alkynes, imines, and organoboron compounds such as alkenyl and aryl boronic acids [462]. The resulting allylic amines are obtained in high regioselectivity. A palladium-catalyzed three-component reaction between allenes, organic halides and boronic acids was reported [463]. A chemo- and regioselective Ru(II)-catalyzed cyclotrimerization involving alkynylboronates and two other alkynes can be

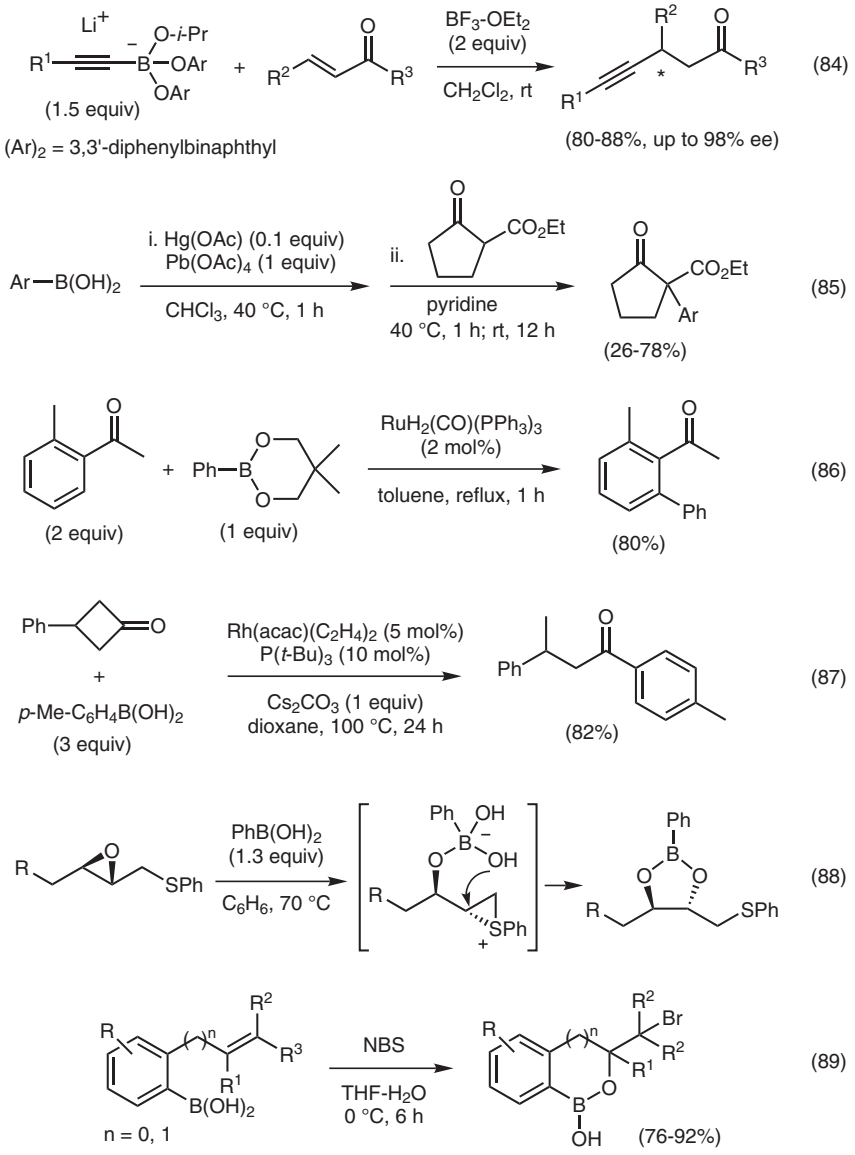


Figure 1.41 Selected examples of other reactions of boronic acid derivatives.

turned into a four-component synthesis of polysubstituted arenes when combined with a one-pot Suzuki coupling (Chapter 9) [464].

Under favorable conditions, the hydroxyl group of boronic acids can serve as a nucleophile. For example, epoxy-sulfides are opened stereoselectively by phenylboronic acid to afford diol products (Equation 88, Figure 1.41) [465]. A new variant of this process makes use of a palladium catalyst [466]. Boronic acids have been employed recently as internal nucleophiles in a bromo-boronolactonization of olefins (Equation 89) [467].

1.6
Overview of other Applications of Boronic Acid Derivatives

1.6.1
Use as Reaction Promoters and Catalysts

By forming transient esters with alcohols, boronic acids can act as catalysts or templates for directed reactions. In the early 1960s, Letsinger demonstrated that a bifunctional boronic acid, 8-quinolineboronic acid, accelerates the hydrolysis of certain chloroalkanols (Equation 90, Figure 1.42) [468], and that boronoarylbenzimidazole serves as catalyst for the etherification of chloroethanol [469]. Mechanisms involving covalent hemiester formation between the boronic acid in the catalyst and the alcohol substrate, combined with a basic or nucleophilic participation of the nitrogen, were invoked. More recently, Yamamoto and co-workers found that several electron-poor arylboronic acids, in particular 3,4,5-trifluorobenzeneboronic acid, catalyze amidation reactions between carboxylic acids and amines [470]. Arylboronic acids catalyze the hydrolysis of salycylaldehyde imines [471], and affect the alkaline conversion of D-glucose into D-fructose [472]. Phenylboronic acid assists in the cyclodimerization of D-glucosamine into a pyrazine [473], and in the photocyclization of benzoin into 9,10-phenanthrenequinone [474].

Narasaka and co-workers demonstrated that phenylboronic acid can be employed to hold the diene and dienophile in such a way that the normal regiocontrol of a Diels–Alder reaction can even be inverted [475]. This templating strategy was elegantly exploited in the synthesis of a key intermediate in the total synthesis of taxol by Nicolaou and co-workers (Equation 91, Figure 1.42) [476]. By a similar trick, phenols are ortho-alkylated with aldehydes through a proposed six-membered transition state where phenylboronic acid, used stoichiometrically, holds the two reactants in place (Equation 92) [477]. Thermolysis of the resulting benzodioxaborinanes affords *ortho*-quinone methides that undergo a wide range of intermolecular cycloadditions and nucleophilic additions [478]. Molander and co-workers have demonstrated the existence of neighboring group participation from a chiral boronate in the reduction of ketones (Equation 93) [479]. A highly ordered cyclic transition structure with boron-carbonyl coordination was invoked to explain the high level of remote stereoinduction. The reduction of imine derivatives was also performed with high selectivity [480].

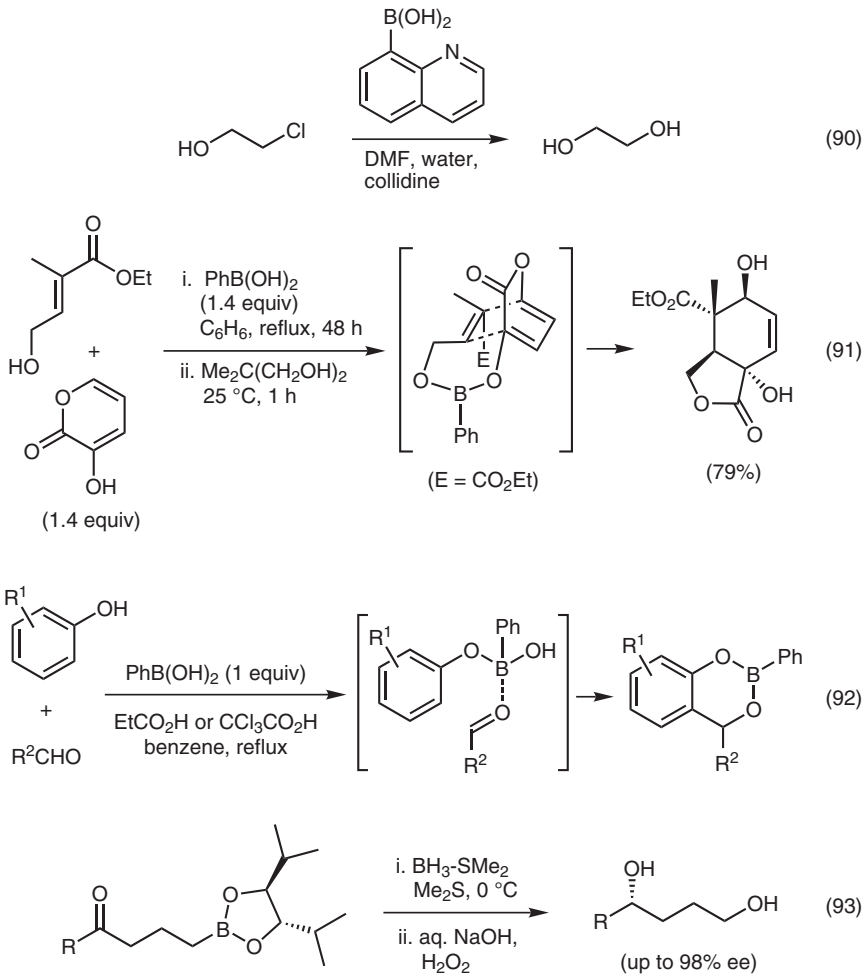


Figure 1.42 Selected examples of applications of boronic acids (esters) as reaction promoters and catalysts.

Boronic acids and their derivatives are very popular as components of chiral Lewis acids and promoters for various reaction processes [481]. Indeed, the chiral acyloxyboranes and the oxazaborolidines (Section 1.2.3.5) described in Chapter 11 made a mark in organic synthesis. Recently, Ryu and Corey extended the application of chiral oxaborolidinium catalysts to the cyanosilylation of aldehydes [482]. Chiral diazaborolidine salts were evaluated in the enantioselective protonation of enol ethers [145]. Likewise, a tartramide-derived dioxaborolane is key as a chiral promoter in the asymmetric cyclopropanation of allylic alcohols [483]. More examples and details on the applications of boronic acid derivatives as reaction promoters and catalysts are provided in Chapter 10.

1.6.2 Use as Protecting Groups for Diols and Diamines

The use of boronic acids to protect diol units in carbohydrate chemistry was demonstrated several decades ago, in particular by the work of Ferrier [484] and Köster [485]. For example, whereas an excess of ethylboronic acid (as the boroxine) leads to a bisboronate furanose derivative of D-lyxose, equimolar amounts provided 2,3-*O*-ethylboranediyl-D-lyxofuranose (Equation 94, Figure 1.43) [486]. From the latter, a regioselective diacetylation reaction followed by treatment with HBr led to the desired α-D-lyxofuranosyl bromide in a very high yield. An alternative method for the preparation of cyclic alkylboronic esters involves treatment of diols with lithium trialkylborohydrides [95]. Phenylboronic esters of carbohydrates have also been exploited in the regioselective sulfation of saccharides [487], and as a way to regioselectively alkylate diol units of pyranosides [488]. The reaction of phenylboronic acids with nucleosides and mononucleotides was described long ago [489]. The *ortho*-acetamidophenyl boronate group was employed to protect the vicinal 1,2-diol of adenosine [312]. It was found to be more resistant to hydrolysis than the corresponding phenylboronate, which was attributed to the beneficial coordination effect of the ortho substituent. Phenylboronic acid has also been used as a protecting group for 1,2- and 1,3-diol units of other natural products [481b], such as terpenes [490] macrolides [491], prostaglandins [492], quinic acid derivatives [493], anthracyclines [494], macrocyclic polyamines [495], and polyether antibiotics [496]. Typically, phenylboronates are made by a simple condensation with a diol, which can be eventually deprotected by exchange with another diol, or by a destructive oxidation with hydrogen peroxide. For example, Evans and co-workers used phenylboronic acid to selectively protect the 1,3-diol unit of a triol (Equation 95, Figure 1.43) [496]. Oxidation of the remaining hydroxyl and oxidative deprotection of the phenylboronate led to a concomitant cyclization to give a pyran product. In a key step to the synthesis of verbacine, the 1,3-diamine unit of a polyazamacrocycle was selectively protected with 3,5-$(CF_3)_2$-$C_6H_3B(OH)_2$ [495]. Recently, a high-yielding solid-state method for the protection of diols, polyols, and diamines with $PhB(OH)_2$ was described [497]. Phenylboronic acid was also employed as an in situ protective reagent in osmium tetraoxide promoted dihydroxylation of alkenes [498]. In this variant, it serves as a water replacement for cleavage of the osmate intermediate, while also providing a nonpolar cyclic boronate derivative that is easier to extract in organic solvents than is the free diol. Sharpless and co-workers applied this "boronate capture" procedure to the dihydroxylation of polyenes (Equation 96), and found several further advantages, such as faster reaction times, minimization of overoxidation, and a marked effect on the diastereoselectivity of these multiple dihydroxylations [499].

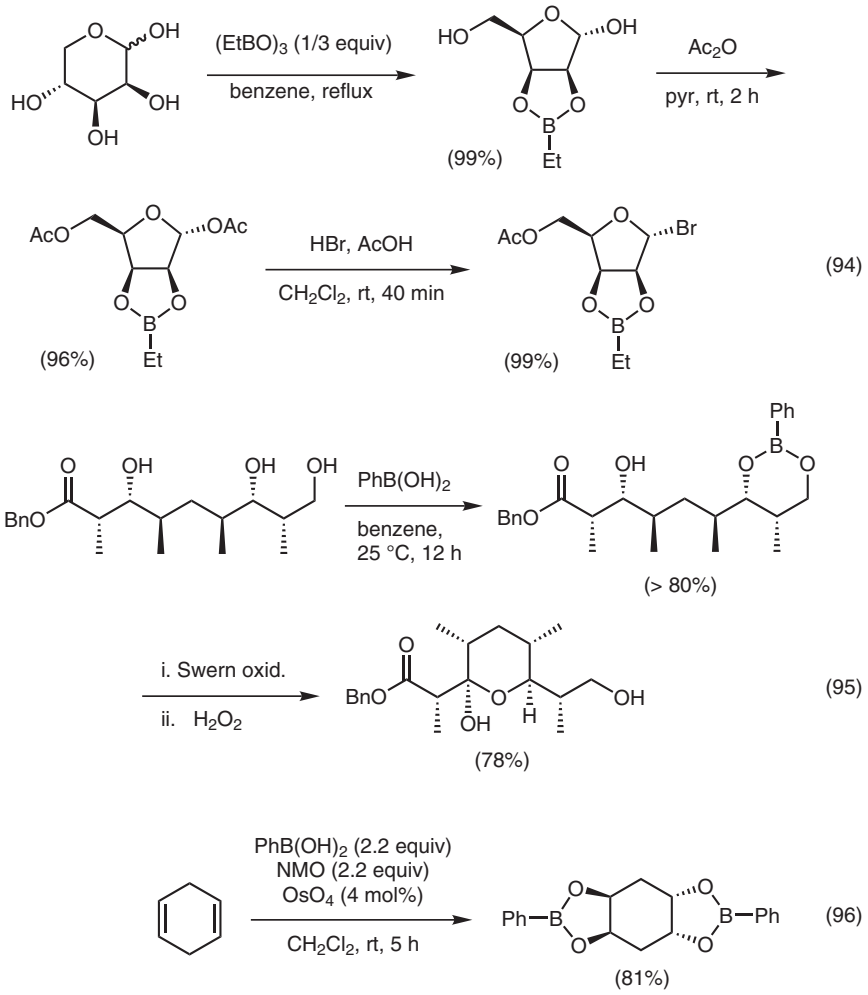


Figure 1.43 Examples of the use of boronic acids for the protection of diol compounds.

1.6.3
Use as Supports for Derivatization and Affinity Purification of Diols, Sugars, and Glycosylated Proteins

The concept of immobilizing diol compounds with a boronic acid conjugated support as a sort of heterogeneous protecting group strategy is the antipode of the diol-based supports described in Section 1.4.2. Examples of such boronic acid matrices include polystyryl boronic acid resins (**120**) [500–502], the cellulose-derived support **121** [503], the methacrylic polymer **122** [504], and the polyacrylamide-supported nitroarylben-

zene boronic acid **123** [505] (Figure 1.44). Applications of immobilized boronic acids have been reviewed, and include the purification or analysis of carbohydrates, diverse nucleic acid derivatives embedding rigid vicinal cis-diols, and catechols, including L-DOPA, catechol estrogens, and catecholamines from urine [506]. One of the most important biomedical uses of immobilized boronic acids is in the separation and quantification of glycosylated proteins [507], such as the level of glycosylated hemoglobin in red blood cells, which is an important indicator for the clinical analysis of diabetes. In one other application, a water-soluble polyacrylamide copolymer was tested as a mitogen for lymphocytes [508]. Other supports have also been considered as components of sensing systems for glucose [509] and nucleotides such as AMP [510]. With hydrogels, the extent of carbohydrate binding can be correlated with swelling (change in volume) [509c]. All of the above arylboronic acid supports demonstrate a selectivity profile similar to their homogeneous counterpart, and only cis-diols of a favorable

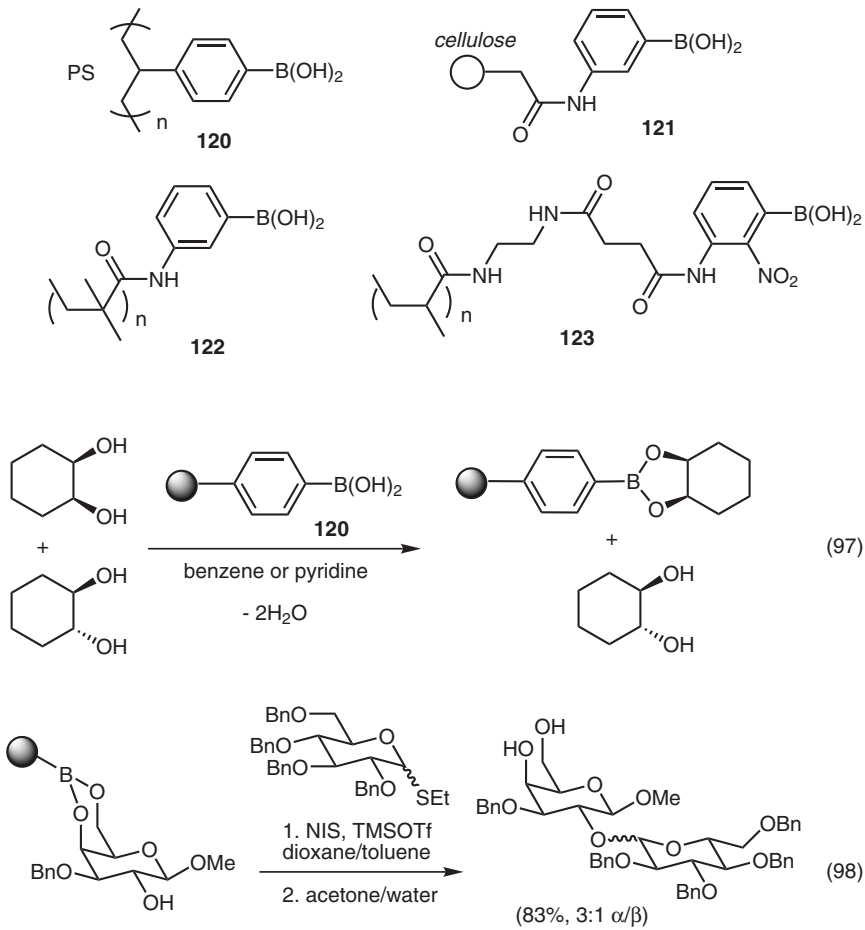


Figure 1.44 Boronic acid supports for diol compounds.

coplanar geometry can be immobilized efficiently. For example, polystyryl boronic acid (**120**) was put to use in the fractionation of carbohydrates and in the separation of isomeric diols [500, 511]. In agreement with the stereochemical arguments discussed in previous sections, of an isomeric mixture of *cis*- and *trans*-1,2-cyclohexenadiol, only the former bound to resin **120**, thereby allowing an effective separation of the two isomers (Equation 97, Figure 1.44) [511]. Among several other examples of applications to the purification of polyol compounds, the boronic acid substituted methacrylic polymer **122** was employed to separate ribonucleosides and deoxyribonucleoside mixtures [504]. The selectivity profile of support **121** in the binding of various nucleic acid and sugar derivatives was studied. Not surprisingly, the heterogeneous boronate formation process in a chromatography column was more efficient at a higher pH, with diols of favorable geometry, and also depended on the ionic strength and the nature of the cations in the eluent [503]. Polyacrylamide support **123** was employed in the purification of transfer ribonucleic acids [505]. Due to the low pK_a (ca. 7) of its electron-poor boronic acid unit, the immobilization process was performed efficiently at neutral pH, and the tRNA was recovered from the column at pH 4.5. In the hope of further increasing affinity and selectivity in carbohydrate binding, the technique of molecular imprinting polymerization was tested with boronic acid containing monomers [61a, 512, 513].

Fréchet and co-workers also demonstrated the utility of resin **120** in the selective immobilization and transformation of carbohydrate derivatives [501a, 514]. Inspired by this work, Boons and co-workers used the same resin as a reusable linker system for the solid-phase synthesis of oligosaccharides (Equation 98, Figure 1.44) [515].

1.6.4
Use as Receptors and Sensors for Carbohydrates and other Small Molecules

The ability of boronic acids to form esters reversibly with cis-diols (Section 1.2.3.2.3) has been a central theme in the intensive area of sensor and receptor development for oligosaccharides [516]. Such molecules can be used for various applications, such as derivatizing agents for the chromatographic detection of carbohydrates and, in particular, in the important global health issue of blood glucose monitoring for diabetes patients. The most recent advances in the field of carbohydrate sensing with boronic acids are reviewed in Chapter 12.

Mixed receptors containing boronic acids and charged functionalities were also developed for the recognition of sugar acids [517] and even for heparin [311], a polysulfated saccharide. Boronic acids also interact strongly with α-hydroxycarboxylic acids [518], and receptors selective for tartrate were reported [519].

1.6.5
Use as Antimicrobial Agents and Enzyme Inhibitors

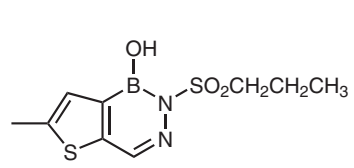
Michaelis and Becker noted the toxicity of phenylboronic acid against microorganisms and its relative harmlessness against higher animals more than a century ago [198]. The antimicrobial properties of simple arylboronic acid derivatives were fur-

ther examined in the 1930s [176]. Interestingly, the activity of arylboronic acids in plants has been investigated thoroughly, and several were found to promote root growth [8, 55]. Several boronic acids and their benzodiaza- and benzodioxaborole derivatives were evaluated as sterilants of house flies [57]. Several boronic acids and esters display potent antifungal activity [520]. For instance, the diazaborine family, exemplified by the thienodiazaborine **124** (Figure 1.45), has long been known to possess potent activity against a wide range of Gram negative bacteria [521]. Initially, this biological effect was ascribed to the inhibition of lipopolysaccharide synthesis [522]. Recent evidence, however, point to a different molecular target, the NAD(P)H-dependent enoyl acyl carrier protein reductase [523]. This enzyme is involved in the last reductive step of fatty acid synthase in bacteria, and the structure of the inhibitory complex with diazaborines in the presence of the nucleotide cofactor was elucidated by X-ray crystallography [524]. Interestingly, the bisubstrate complex shows a covalent bond between boron, in a tetracoordinate geometry, and the 2′-hydroxyl of the nicotinamide ribose. In addition to their potential in the fight against microbial resistance in *Mycobacterium tuberculosis* and other strains, diazaborine compounds such as a recently reported estrogen mimic may find other medicinal applications [525]. A prostaglandin mimetic in which a boronyl group replaces the carboxylate, **125**, was found to be moderately active [526].

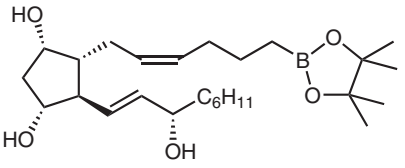
Boronic acids inhibit hydrolytic enzymes such as serine proteases [527], and the efficiency of a sepharose-based arylboronic acid sorbent in the chromatographic purification of this class of enzymes has been demonstrated [528]. In the development of boronic acid based enzyme inhibitors as pharmaceutical drugs, target specificity within a wide family is crucial to avoid side effects. The development of the α-aminoalkylboronic acid analogues of α-amino acids was key in the recent development of potent peptidylboronic acid analogues with improved specificity (Chapter n). The usual mechanism of inhibition is the formation of a tetracoordinate boronate complex (**126**, Figure 1.45) by coordination of the side chain hydroxyl nucleophile of the active serine residue, thus mimicking the tetrahedral intermediate for amidolysis [529]. Other modes of inhibition have been identified, however, like the formation of covalent adducts with the serine or histidine residues of the active site [530, 531]. This intensive area of medicinal chemistry research, reviewed in Chapter 13, has recently culminated in the commercialization of the peptidylboronic acid antineoplastic drug Velcade (**127**) [532, 533]. The latter has recently been approved by the United States FDA for treatment of relapsed and refractory multiple myeloma.

1.6.6
Use in Neutron Capture Therapy for Cancer

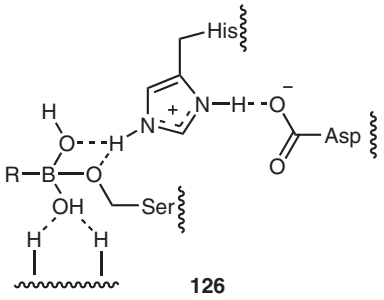
Several boronic acids such as 4-boronophenylalanine have been evaluated as sources of boron for their potential use in a form of brain cancer therapy based on the technology of soft neutron capture [534]. This topic is also reviewed in Chapter 13.



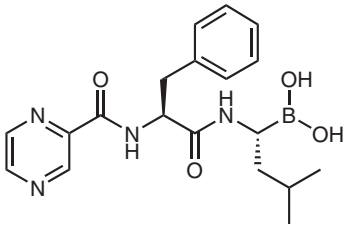
124



125



126



127

Figure 1.45 Examples of biologically active boronic acids. Note: **127** is the dipeptidyl boronic acid antineoplastic drug Velcade®, a selective proteasome inhibitor.

1.6.7
Use in Transmembrane Transport

As first demonstrated with monosaccharides by Shinbo and co-workers, the ability of boronic acids to complex diols can be exploited in the study of molecular transport across lipophilic membranes [535]. Compounds that possess such carrier properties have potential applications in drug delivery. For example, Mohler and Czarnik demonstrated the ability of a cholanyl 3-pyridiniumboronic acid derivative (**128**, Figure 1.46) to transport ribonucleosides across a dichloroethane liquid membrane [536]. Other examples of boronic acid based systems include a three-component amino acid transport system [537], the cathecholamine transporter **129** [538], and various carriers for monosaccharides such as fructose [54]. In fact, one of the most important potential applications of boronic acid carriers is in the area of development of selective fructose-permeable liquid membranes, which was reviewed recently [539]. D-Fructose is the sweetest and most valuable of all common natural sweeteners. Its current production as a "high fructose corn syrup", enriched from crudes containing other sugars, is an energy-intensive industrial process that involves the evaporation of large quantities of water. The use of membrane-based technology could be highly advantageous due to its potential amenability to a continuous automated process. Interested readers will find a more detailed account on the use of boronic acids in membrane transport in a review by Smith and Gardiner [540].

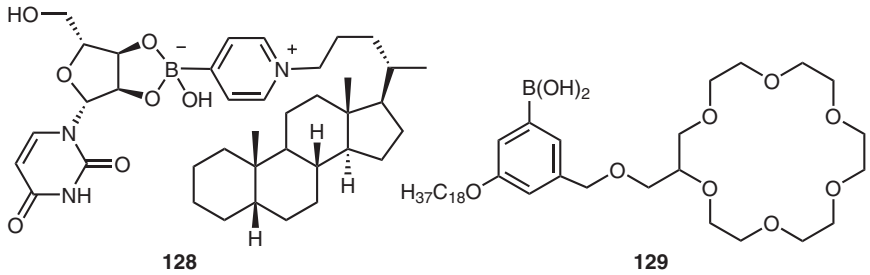


Figure 1.46 Examples of boronic acid based transporters.

1.6.8
Use in Bioconjugation and Labeling of Proteins and Cell Surface

Proteins and enzymes can be covalently linked to 3-aminophenylboronic acid, and the resulting conjugates were shown to bind to small cis-diol molecules and glycated hemoglobin [541]. Studies both in solution and using gel chromatography confirmed the low affinity of the boronate interaction. To address this problem, a conjugation method was developed based on the relatively stronger salicylhydroxamic acid–boronate interaction [150, 542]. As demonstrated with the diboronic acid–alkaline phosphatase conjugate **130** (Figure 1.47), higher affinity over a wider range of pH can be achieved by taking advantage of polyvalent interactions with the complexing sepharose support.

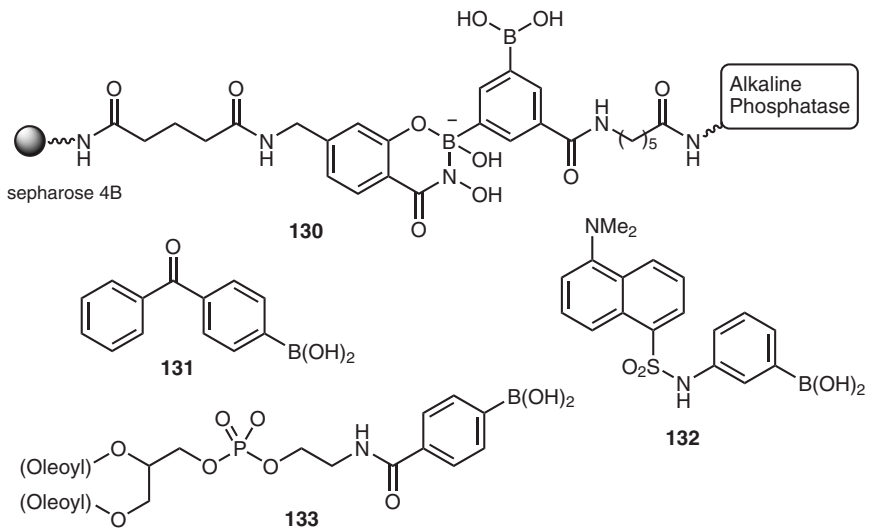


Figure 1.47 Boronic acid compounds used in protein labeling and conjugation.

A benzophenone boronic acid, **131**, was recently employed for probing altered specificity of chemically modified mutant subtilisin enzymes by photoaffinity labeling [543]. As discussed in Section 6.3, boronic acid supports can be employed to purify glycohemoglobin. A related soluble and colored arylboronic acid was reported for the quantification of these proteins [544]. More than two decades ago, a dansyl-labeled arylboronic acid (**132**) was reported to bind to the cell wall of the bacteria *B. subtilis*, presumably via boronate ester formation with the sugar coating [545]. In the same study, a diboronic acid was found to agglutinate erythrocytes. Recently, Smith and co-workers designed liposomes containing a phospholipid bearing an arylboronic acid (e.g., **133**), and demonstrated the binding of these liposomes to erythrocytes, presumably through interaction with the glycocalyx [546]. Likewise, diboronic acid sensors were reported to bind to tumor cells overexpressing the fucosylated sialyl Lewis X trisaccharide (Chapter 13) [547]. Recently, a fluorescein-based diboronate dye was shown to act as a selective, cell-permeable probe for hydrogen peroxide in living cells [548].

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2
Metal-catalyzed Borylation of Alkanes and Arenes via C–H Activation for Synthesis of Boronic Esters

Tatsuo Ishiyama and Norio Miyaura

2.1
Introduction

Organoboron derivatives are an important class of compounds that have been utilized as synthetic intermediates [1–6], functional molecules [7–9], functional polymers [10], ^{10}B carriers for neutron capture therapy [11], and biologically active agents [12]. A traditional method for their synthesis is the alkylation of trialkylborates or haloboranes with organomagnesium or -lithium reagents (transmetalation) [1, 13] or addition of hydroboranes to unsaturated hydrocarbons (hydroboration) [1, 14]. Although these methods are now common for large-scale preparations of organoboron compounds, catalyzed reactions are an interesting strategy for obtaining chemo-, regio-, and stereoselectivities that differ from those achieved by uncatalyzed reactions. For example, catalyzed hydroboration of alkenes and alkynes [15] with catecholborane (HBcat, cat = $O_2C_6H_4$) or pinacolborane (HBpin, pin = $Me_4C_2O_2$) has provided a method for asymmetric hydroboration of alkenes with chiral phosphine-rhodium catalysts [16], 1,4-hydroboration of 1,3-dienes [17], trans-hydroboration of terminal alkynes giving (*Z*)-1-alkenylboronates [18], or diastereoselective hydroboration of cyclic and acyclic allyl alcohol derivatives [19]. A protocol that involves oxidative addition of an H–B bond to a low-valent transition metal has been successfully extended to analogous metal-catalyzed addition reactions of B–B [20], B–S [21], B–Si [22] or B–Sn [23] compounds [15c].

Conversely, cross-coupling reactions of B–B [15c, 20] or B–H [24] reagents with aryl, vinyl, allyl and benzyl halides or triflates have provided a direct method for the borylation of organic electrophiles without using lithium or magnesium intermediates. Because of the availability of various electrophiles and mild reaction conditions, this method has allowed convenient access to organoboron compounds that have a variety of functional groups. An extension of this methodology to aliphatic or aromatic C–H borylation is of significant value for direct preparation of organoboron compounds from various hydrocarbons [25]. Some key mechanistic steps in putative catalytic cycles have been established recently via stoichiometric C–H borylation of alka-

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nes, arenes and alkenes with (boryl)metal complexes [26, 27]. Those discoveries were followed by the rapid development of catalytic processes for C–H borylation of hydrocarbons with bis(pinacolato)diboron (B_2pin_2) or pinacolborane [20]. In most of these reactions, it is widely recognized that the catalytic cycle involves a (boryl)metal species originating by transmetalation or oxidative addition. The synthesis, characterization, bonding, and reactivity of these catalytically important species have been reviewed [28]. There have also been extensive theoretical studies on the M–B bond and its role in catalytic cycles [29].

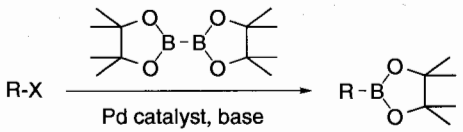
2.2 Borylation of Aromatic Halides and Triflates

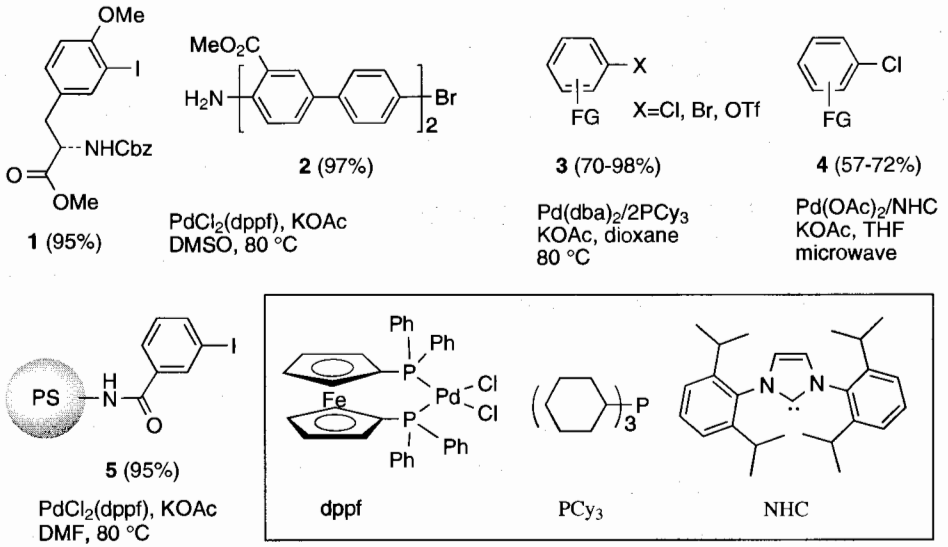
2.2.1 Cross-coupling Reaction of Diborons

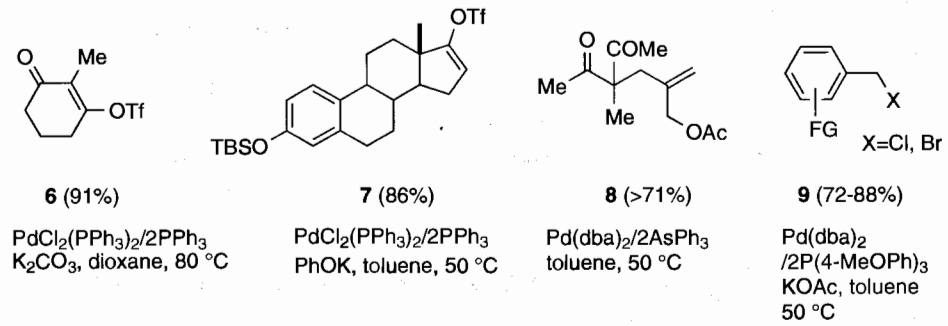
Metal-catalyzed cross-coupling reactions of disilanes [30] and distannanes [31] have been successfully used for the synthesis of organosilicon and -tin compounds from organic halides. The lack of suitable boron nucleophiles has limited this protocol for boron compounds, but tetra(alkoxo)diborons such as bis(pinacolato)diboron (B_2pin_2) acts as boron-nucleophiles for palladium-catalyzed cross-coupling reactions of organic halides and triflates (Scheme 2.1) [15c, 20]. Coupling reactions of diborons with aromatic halides [32, 33] and triflates [34] directly provide arylboronic esters. The presence of a base such as KOAc is critical for coupling reactions of diborons, suggesting a transmetalation between B_2pin_2 and the Ar-Pd-OAc intermediate that is generated by displacement of X in Ar-Pd-X with an acetate anion [32]. Since strong bases such as K_3PO_4 and K_2CO_3 prompt the competitive formation of homocoupling biaryls (36–60% yields), KOAc is recognized to be a suitable base for a wide variety of aromatic substrates, including aryl iodides [32, 35], bromides [32, 36, 38], chlorides [33, 37] and triflates [34]. Although $PdCl_2$(dppf) works well as a catalyst for representative aromatic iodides and bromides (e.g., **1** and **2** in Scheme 2.1) [32], electron-donating PCy_3 [33] and an N-heterocyclic carbene (NHC) [37] complex are advantageous for achieving high yields within a short reaction time for aryl chlorides and electron-rich aryl bromides or triflates (e.g., **3**, **4**). These ligands are also effective for preventing the participation of phosphine-bound aryls, which will competitively occur when PPh_3 and dppf are used as a ligand. The reaction can be further accelerated by irradiation with microwaves [37]. The reaction also offers a method for synthesizing boronic esters in the solid phase. For example, a polymer-bound boronate is quantitatively obtained by treating an iodobenzamide supported on polystyrene (**5**) with the diboron reagent at 80 °C for 20 h in the presence of $PdCl_2$(dppf) and KOAc [39]. Subsequent coupling with haloarenes, followed by hydrolysis with trifluoroacetic acid, furnishes various biaryls for parallel synthesis and combinatorial synthesis.

In the synthesis of 1-alkenylboronic acids or esters from the corresponding magnesium or lithium reagents, it is often difficult to retain the stereochemistry of start-

ing 1-alkenyl halides and the required protection–deprotection of sensitive functional groups is a tedious process. Borylation of 1-alkenyl halides or triflates with diborons proceeds with complete retention of alkene stereochemistry and is compatible with various functional groups [40, 41]. The reaction requires a stronger base than that for aryl halides in the presence of triphenylphosphine-palladium catalysts. Fine K_2CO_3 suspended in dioxane is recommended for triflates conjugated to a carbonyl







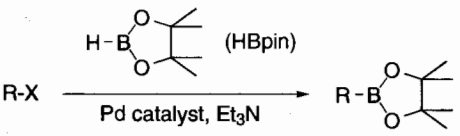
Scheme 2.1 Organoboron compounds via cross-coupling reactions of diborons.

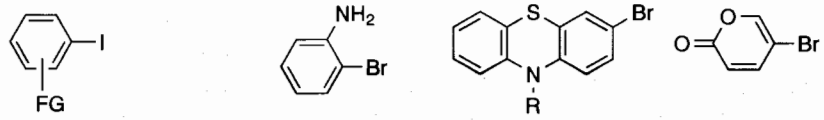
group (**6**) [41] and KOPh suspended in toluene for unactivated/unconjugated bromides or triflates (**7**) [40]. Pinacol alkenylboronates thus obtained can be isolated by chromatography on silica gel without decomposition or they can be directly used for the cross-coupling reactions without isolation of the boron intermediates.

Allylboron compounds are valuable reagents in organic synthesis since their diastereoselective addition to a carbon–oxygen or the carbon–nitrogen double bond provides homoallylic alcohols or amines via a chair-like, six-membered cyclic transition state [1]. Such allylborations of pinacol ester derivatives are very slow due to their steric hindrance, however, the reaction takes place at –78 °C in the presence of $AlCl_3$ or $Sc(OTf)_3$ (10 mol%) [42]. Palladium(0)-catalyzed cross-coupling reactions of diboron with allyl acetates such as **8** provide variously functionalized allyboron compounds (Scheme 2.1) [43, 44]. The boron atom couples at the less-hindered terminal carbon to provide thermally stable (*E*)-allylboronates via a *syn*-π-allylpalladium intermediate [43]. Various 5-5, 6-5, and 7-5 *cis*-fused exomethylene cyclopentanols are directly obtained from β-ketoesters or diketones via a cross-coupling/intramolecular allylboration sequence [44]. Benzyl chlorides and bromides such as **9** are borylated with B_2pin_2 in the presence of a palladium(0)-tris(*p*-methoxyphenyl)phosphine catalyst and KOAc [45].

2.2.2
Cross-coupling Reaction of Pinacolborane

Pinacolborane (HBpin) is a unique, economical boron nucleophile for borylation of aryl and 1-alkenyl halides or triflates that is recommended for large-scale preparations [24] (Scheme 2.2). Interestingly, various reducible functional groups in **10** remain intact during the reaction at 80 °C; however, the reaction is generally accompanied by the formation of some undesirable dehalogenation products (ArH, 10–20%). Borylation of 2-bromoaniline (**11**) [46] or bromophenothiazine (**12**) [47] is directly followed by cross-coupling with haloarenes in high yields. The ester group of **13** remains intact at 120 °C in the synthesis of 2-pyrone-5-boronate [48]. The bisporphyrin-based synthetic receptor that has a molecular weight of 4198 is synthesized by a sequential double cross-coupling reaction. Borylation of bromoporphyrin (**14**) with pinacolborane is followed directly by cross-coupling with 1,3-diiodobenzene to give a bisporphyrin receptor [49]. The presence of Et_3N plays a key role in not only preventing the production of ArH but also facilitating the B–C bond formation. The mechanism is unknown, but the displacement of Pd(II)–X with a weakly nucleophilic boryl anion ($Et_3NH^+Bpin^-$) or σ-bond metathesis between H-Pd-Bpin and ArX have been proposed for the process leading to the formation of an Ar-Pd-Bpin intermediate [24].



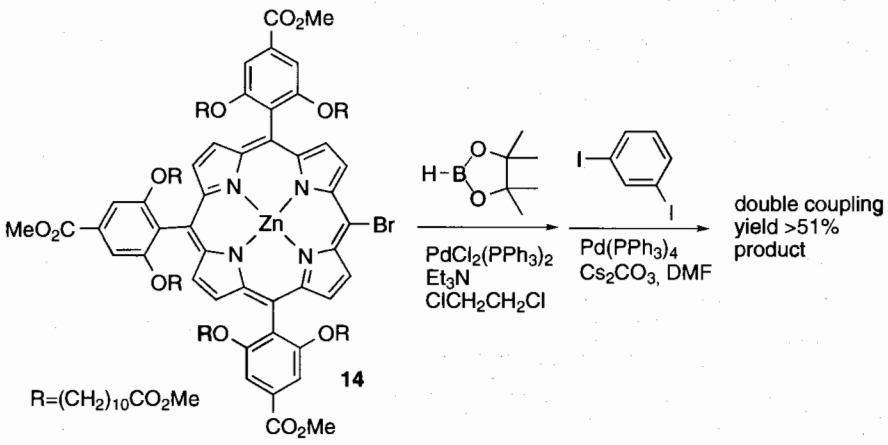


10, 77-84%
$PdCl_2(dppf)$ or $PdCl_2(PPh_3)_2$
Et_3N, dioxane, 80 °C
(FW=4-MeO, 4-Me_2N
4-NO_2, 4-EtO_2C)

11 (81%), $Pd(OAc)_2$
/(*o*-biphenyl)PCy_2
Et_3N, dioxane,
80 °C

12, 73-77%
$PdCl_2(PPh_3)_2$
Et_3N, dioxane
reflux

13, 70%
$PdCl_2(PPh_3)_2$
Et_3N, toluene
reflux



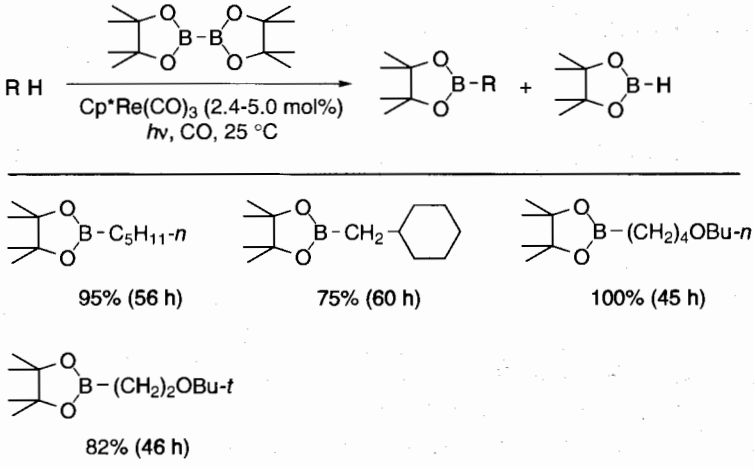
Scheme 2.2 Arylboron compounds via coupling reaction of pinacolborane.

2.3
Aliphatic C–H Borylation

Simultaneous C–H activation and functionalization of hydrocarbons allows abundant, inert hydrocarbons to serve as direct feedstocks for functionalized compounds [50]. The versatility of organoboron compounds in organic synthesis makes the borylation of hydrocarbons an attractive goal [20, 25–27].

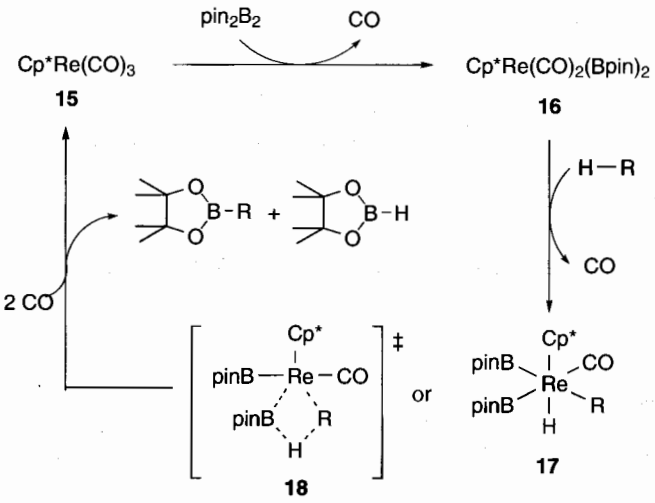
2.3.1
Re-catalyzed Photochemical Reaction

C–H borylation of alkanes was first demonstrated by Hartwig using photochemical activation of $Cp^*Re(CO)_3$ (Scheme 2.3) [51]. With irradiation from a 450 W medium-pressure Hanovia mercury arc lamp, alkylboronates are obtained by direct borylation of alkanes with pin_2B_2 in the presence of $Cp^*Re(CO)_3$ (2.4–5.0 mol%) and CO (2 atm). Pinacolborane is not effective for the borylation; thus, one of two boron atoms participated in the catalytic cycle. All reactions resulted in high regiospecificity for the functionalization of terminal primary carbons.



Scheme 2.3 Aliphatic C–H borylation with Cp^*Re complexes.

Reaction of $Cp^*Re(CO)_2(Bpin)_2$ (**16**), prepared from $Cp^*Re(CO)_3$ (**15**) and pin_2B_2, led to the regiospecific formation of 1-borylpentane in quantitative yield under irradiation of light in pentane. Thus, the catalytic cycle involves oxidative addition of pin_2B_2 to $Cp^*Re(CO)_3$ with photochemical dissociation of CO, oxidative addition of C–H bond to $Cp^*Re(CO)_2(Bpin)_2$ (**16**) giving a rhenium(V) intermediate (**17**), and finally reductive elimination of an alkylboronate with association of CO (Scheme 2.4) [51]. The interaction required for C–H activation of alkane with **16** is not known; but higher reactivity of primary over secondary C–H bonds has been reported in both oxidative addition (**17**) and σ-bond metathesis (**18**) processes [52]. Isomerization of a sec-alkyl group in $Cp^*Re(H)(R)(CO)(Bpin)_2$ (**17**) to an *n*-alkyl isomer before reductive elimination of pinB-R is another probable process that has been reported in metal-catalyzed hydroboration of internal alkenes [15c].

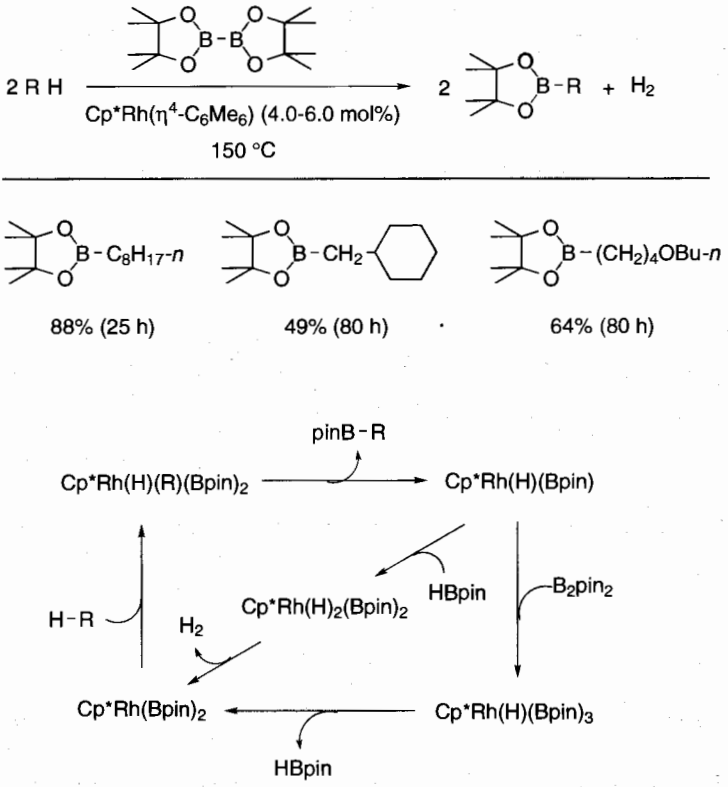


Scheme 2.4 Catalytic cycle for aliphatic C–H borylation with Cp*Re complexes.

2.3.2
Rh-catalyzed Reaction

A practical method for direct borylation of non-activated alkanes by Rh catalysts was first reported by Hartwig (Scheme 2.5) [53]. Among the catalysts employed, which included Cp^*IrH_4, $Cp^*Ir(C_2H_4)_2$, $Cp^*Rh(C_2H_4)_2$, $Cp^*Rh(C_2H_3SiMe_3)_2$, $Cp^*Rh(H)_2(SiEt_3)_2$ and $Cp^*Rh(\eta^4\text{-}C_6Me_6)$, the hexamethylbenzene complex exhibited greater long-term activity with a low catalyst loading. Again, alkanes regiospecifically reacted at the terminal carbon with pin_2B_2 at 150 °C. In the presence of $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ (4.0–6.0 mol%), 1 equiv of pin_2B_2 afforded almost 2 equivs of 1-borylalkanes, thus indicating participation of pinBH in the catalytic cycle. Indeed, pinBH in *n*-octane gave pinacol *n*-octylboronate in 65% yield.

^{11}B NMR spectra of reactions of pin_2B_2 with $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ in *n*-octane at high catalyst loadings exhibit a resonance at 40 ppm, which is identical to that of *trans*-$[Cp^*Rh(H)_2(Bpin)_2]$ prepared from *trans*-$[Cp^*Rh(H)_2(SiEt_3)_2]$ and pin_2B_2. The *trans*-$[Cp^*Rh(H)_2(Bpin)_2]$ thus obtained reacted with *n*-octane, giving 2 equivalents of 1-boryloctane in 90% yield, thus suggesting that *trans*-$[Cp^*Rh(Bpin)_2]$ is chemically and kinetically competent to be an intermediate in the catalytic process. The mechanism has been proposed to be an Rh(III)–Rh(V) cycle involving oxidative addition of pin_2B_2 or pinBH to $Cp^*Rh(H)(Bpin)$, reductive elimination of H_2 or pinBH to form an $Cp^*Rh(Bpin)_2$, oxidative addition of an alkane giving $Cp^*Rh(H)(R)(Bpin)_2$, and reductive elimination of a 1-borylalkane (RBpin) to regenerate the $Cp^*Rh(H)(Bpin)$ (Scheme 2.5) [53]. These processes are supported by the results of recent theoretical studies by Miyamoto [54]. The unusual thermodynamic properties of boron reagents



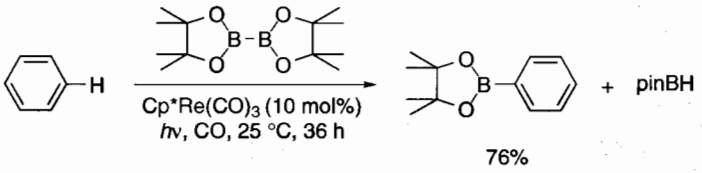
Scheme 2.5 Aliphatic C–H borylation with Cp*Rh complexes.

provide the driving force for the overall process. In the initial stage of the reaction between R–H and pin_2B_2, the B–C (112 kcal mol^{-1}) and B–H (111 kcal mol^{-1}) bonds formed are 21 kcal mol^{-1} stronger than the B–B (104 kcal mol^{-1}) and C–H (98 kcal mol^{-1}) bonds that are broken. The second stage of the reaction between R–H and pinBH is also slightly exothermic since the formation of B–C and H_2 (104 kcal mol^{-1}) are 7 kcal mol^{-1} stronger than the B–H and C–H bonds that are broken.

2.4
Aromatic C–H Borylation

2.4.1
Re-catalyzed Photochemical Reaction

Borylation of benzene by pin_2B_2 takes place under the same conditions as those used for aliphatic C–H borylation (Scheme 2.6) [51]. The reaction may proceed through a mechanism similar to that postulated for aliphatic C–H borylation.

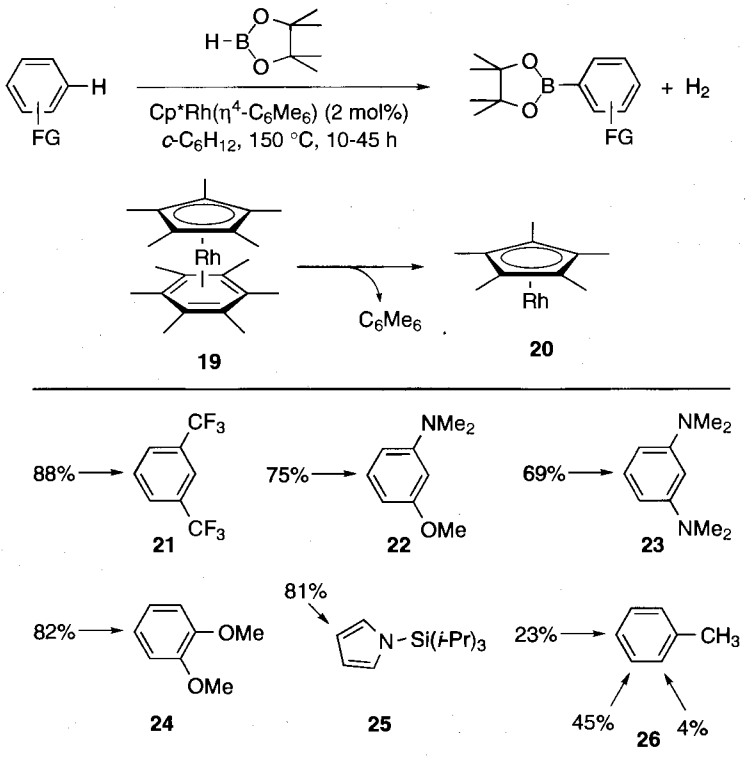


Scheme 2.6 Aromatic C–H borylation with Cp*Re complexes.

2.4.2
Rh-catalyzed Reactions

Under conditions similar to those used for aliphatic C–H borylation, rhodium complexes catalyze the borylation of arenes by pin_2B_2 [53]. $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ (**19**), which in situ generates a coordinatively unsaturated rhodium species (**20**) active for oxidative addition, was found to be the best catalyst, giving a 92% yield after 2.5 h with 5 mol% catalyst loading and an 82% yield (328 turnover number of the catalyst, TON) with 0.5 mol% loading at 150 °C.

Aromatic borylation by pinBH with Hartwig's catalyst $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ was amply demonstrated by Smith (Scheme 2.7) [55, 56]. In cyclohexane as solvent at 150 °C in a sealed ampoule, 1,3-disubstituted arenes were selectively borylated at the 5-position (**21**–**23**) and 1,2-disubstituted arenes (**24**) were borylated at the 4-position. The reaction took place at the α-carbon for pyrrole, but the steric hindrance of the N-triisopropylsilyl group in **25** forced the coupling position to the β-carbon. Monosubstituted arenes (e.g., **26**) resulted in a mixture of para- and meta-coupling products. Thus, the coupling reaction occurs at the less hindered C–H bond to avoid steric hindrance of the substituents. $Cp^*Rh(\eta^4\text{-}C_6Me_6)$ provides significantly higher turnover numbers than the corresponding Ir catalysts, but the iridium catalysts, such as $Cp^*Ir(PMe_3)(H)(Bpin)$ [57], are more selective for alkylarenes and (trihalomethyl)-arenes because the rhodium catalysts react at benzylic C–H bonds and aliphatic C–halogen bonds. Aromatic C–H borylation by pinBH with an Rh catalyst was also studied briefly by Marder [58]. The reaction of pinBH in benzene at 140 °C in the presence of $RhCl\{P(i\text{-}Pr)_3\}_2(N_2)$ (0.3 mol%) affords pinacol phenylboronate in 67% yield. Although the catalyst gives benzylic boronates for alkylbenzenes, $[Cp^*RhCl_2]_2$ was selective for aromatic C–H borylation.

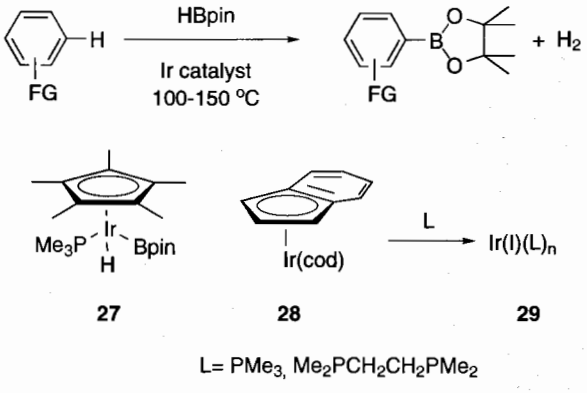


Scheme 2.7 Aromatic C–H borylation with Cp^*Rh complexes.

2.4.3
Iridium-catalyzed Reactions

Iridium(I)-catalyzed aromatic C–H bond borylation with pinacolborane (HBpin) and its mechanism have been studied extensively by Smith [57]. Iridium complexes (**27**, **28**) themselves are inefficient, but addition of a small electron-donating phosphine such as PMe_3 or chelating dmpe [1,2-bis(dimethylphosphino)ethane] to give an iridium(I)-phosphine complex (**29**, Scheme 2.8) substantially increases catalyst activity and turnover number [57a]. The maximum turnover number achieved in the borylation of benzene with HBpin at 150 °C in a sealed ampoule is 4500 [57a].

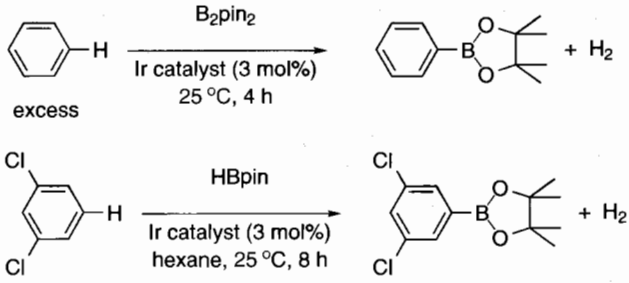
A class of iridium(I) complex (**30**) possessing 2,2′-bipyridine (bpy) or 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) ligands exhibits excellent activity and selectivity for aromatic C–H borylation with B_2pin_2 [59] or HBpin [60]. An Ir catalyst prepared from $\frac{1}{2}[IrCl(COD)_2]_2$ (COD = 1,5-cyclooctadiene) and dtbpy achieves a maximum turnover number (8000) with 0.02 mol% catalyst loading at 100 °C. The reaction was first demonstrated at 80–100 °C using an Ir–Cl complex, but was found to proceed smoothly even at room temperature when the catalyst is prepared from

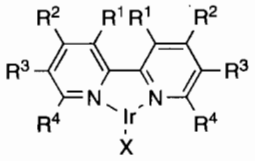


Scheme 2.8 Aromatic C–H borylation.

½[Ir(OMe)(COD)]$_2$ and dtbpy (Scheme 2.9) [61]. Thus, there is a large effect from the anionic ligands (X in **30**) on catalyst activity [61]. Halide and cationic complexes (X = Cl or BF_4) do not catalyze the reaction at room temperature (entry 1), but iridium(I) complexes possessing an OH, OPh, or OMe ligand lead to completion within 4 h (entries 3–5). The reaction of pinacolborane in hexane also takes place at room temperature under analogous conditions using an Ir(OMe) precursor. The high catalyst efficiency of (hydroxo)- or (alkoxo)iridium complexes can be attributed to their more facile conversion into (boryl)iridium complexes compared to the (halo)iridium complexes (as is discussed in the mechanistic section). Among bipyridine derivatives employed, 3,3′-dimethylbipyridine (R^1 = Me), which features a twist between the two pyridyl units, is less active (entry 6), and a 6,6′-dimethyl derivative (R^4 = Me) does not promote the reaction due to increased steric hindrance around the iridium metal center (entry 7) [61]. An investigation of the electronic effect of 4,4′-disubstituted derivatives shows the superiority of electron-rich bipyridines containing NMe_2, OMe, or *t*-Bu substituents compared to the Cl or NO_2 derivatives for both coupling reactions of diboron and pinacolborane (entries 8–13). Among the catalysts examined, the dtbpy complex (R^4 = *t*-Bu) shows a high efficiency for most arenes, including heteroaromatic compounds (entry 10).

The borylation of arenes with B_2pin_2 [59, 61] or HBpin [60] proceeds at room temperature in the presence of an [Ir(OMe)(cod)]$_2$-2dtbpy catalyst (3 mol% for Ir), and various functional groups are tolerated (Scheme 2.10). The reaction is suitable for arenes possessing OMe, I, Br, Cl, CO_2Me, CN, and CF_3 substituents or benzylic C–H bonds. Interestingly, the reaction selectively takes place at the much stronger C–H bond in preference to a C–I bond (entry 3). Both 1,2- and 1,4-disubstituted arenes bearing identical substituents yield the corresponding borylarenes as single isomers (entries 1 and 2). 1,3-Disubstituted arenes are borylated at the common meta position; therefore, isomerically pure products are obtained even with arenes containing two distinct substituents (entries 3–6). Under conditions analogous to those used for typical arenes, heteroarenes are also borylated with B_2pin_2 or HBpin (entries 7–13) [59b, 60, 61b]. Five-membered heteroarenes such as thiophene, pyrrole, furan and their deriv-



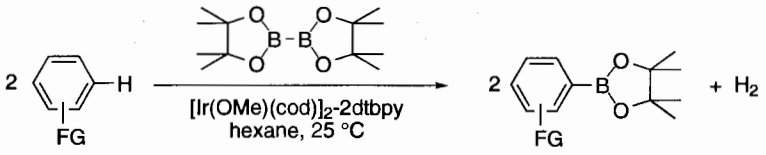


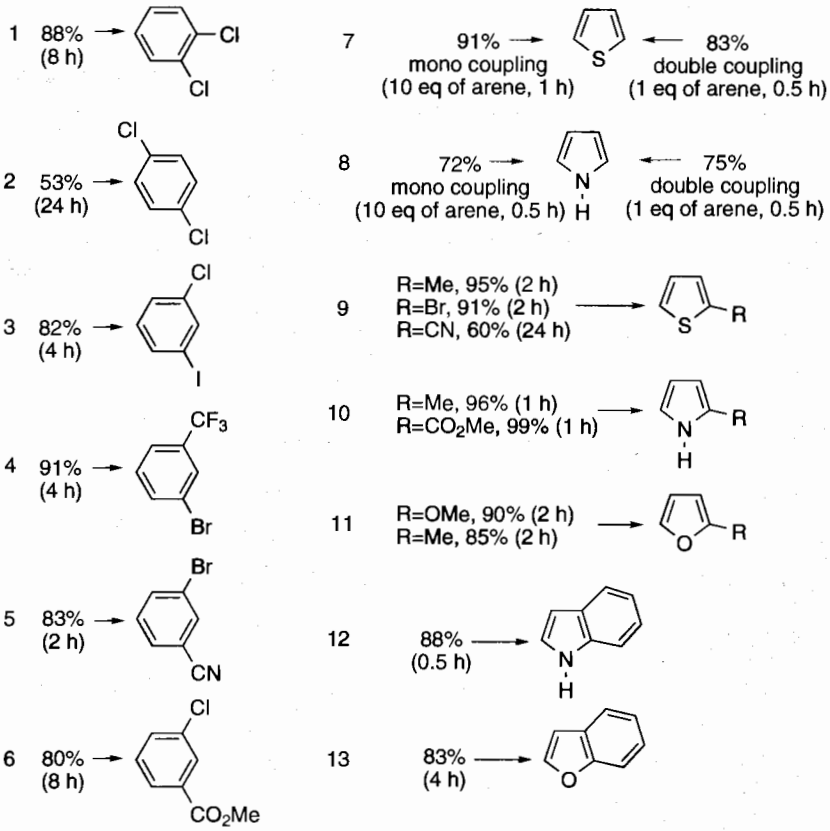
30

entry	IrX	R^1	R^2	R^3	R^4	B_2pin_2 yield/%	HBpin yield/%
1	IrCl(COD)	H	H	H	H	0	-
2	Ir(OAc)(COD)	H	H	H	H	1	-
3	Ir(OPh)(COD)	H	H	H	H	84	-
4	Ir(OH)(COD)	H	H	H	H	88	-
5	Ir(OMe)(COD)	H	H	H	H	90	49
6	Ir(OMe)(COD)	Me	H	H	H	48	8
7	Ir(OMe)(COD)	H	H	H	Me	0	1
8	Ir(OMe)(COD)	H	NMe_2	H	H	88	88
9	Ir(OMe)(COD)	H	OMe	H	H	90	27
10	Ir(OMe)(COD)	H	*t*-Bu	H	H	83	86
11	Ir(OMe)(COD)	H	Me	H	H	89	75
12	Ir(OMe)(COD)	H	Cl	H	H	0	7
13	Ir(OMe)(COD)	H	NO_2	H	H	0	0

Scheme 2.9 Effect of ligands on the efficacy of Ir catalysts.

atives are selectively borylated at the α-carbon of a heteroatom. Reactions of pyrrole, thiophene and furan, which have two active C–H bonds, result in a mixture of mono-borylation and di-borylation products. Monocoupling products are predominant when 10 equivalents of a substrate is used toward B_2pin_2. Conversely, 2,5-diboryl compounds are formed selectively when equimolar amounts of heteroarenes and B_2pin_2 are reacted (entries 7 and 8), while mono-borylation occurs selectively for 2-substituted five-membered heteroarenes (entries 9–11) and benzo-fused het-



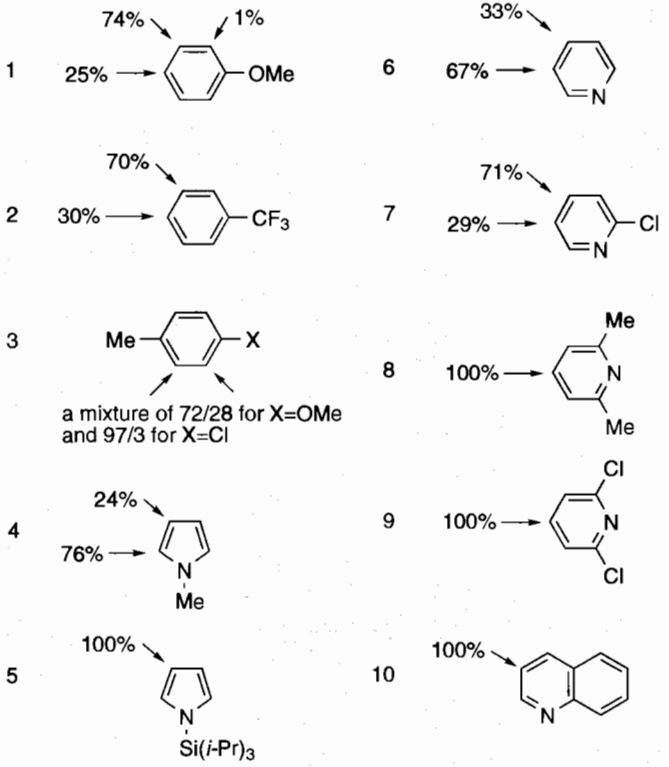


Scheme 2.10 Aromatic C–H borylation with [Ir(OMe)(COD)]$_2$·2dtbpy catalyst at room temperature.

eroarenes (entries 12 and 13). Most reactions of five-membered heteroarenes are complete within 1–2 h at room temperature, which is much faster than the borylation of typical aromatic compounds.

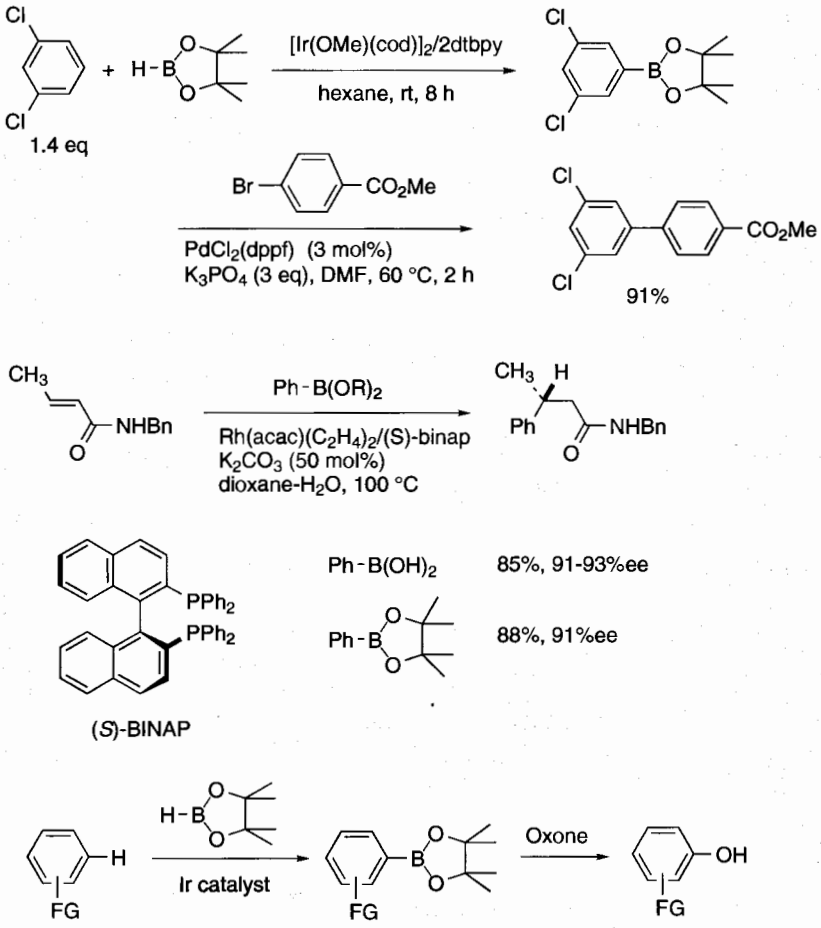
Scheme 2.11 shows the orientation of aromatic C–H borylation. The proportion of coupling products at the ortho carbon is negligible because of the high sensitivity of the catalyst to steric hindrance, and the reaction rather results in a mixture of meta and para products in statistical ratios (ca. 2:1) for mono-substituted arenes (entries 1–3) [59–61]. The reaction behaves as a nucleophilic substitution of aromatic C–H bonds. Thus, trifluoromethylbenzene reacts 6-times faster than anisole, but such

electronic properties of the substituents do not influence significantly the regioselectivities of the substitution. Orientation can be controlled by varying the steric hindrance of substituents. For example, orientation changes from a selective borylation at the 2-position of pyrrole to a mixture of 2- and 3-boryl derivatives for *N*-methylpyrrole (entry 4), and to a selective 3-borylation of *N*-triisopropylsilylpyrrole (entry 5). The orientation of pyridine derivatives shows a different regioselectivity than those of five-membered compounds. Since unsubstituted pyridine has an exceptionally strong coordination ability for Lewis acids, including transition metals, the reaction does not proceed at room temperature. The reaction results in a mixture of 3- and 4-borylpyridine in 42% yield when carried out at 100 °C (entry 6). In contrast, monosubstitution at an α-carbon effectively blocks the coordination of pyridines to allow a smooth reaction at room temperature. For example, 2-chloropyrine yields a mixture of 4- and 5-borylpyridine (entry 7), and 2,6-disubstituted derivatives give 4-borylpyridines at room temperature (entries 8 and 9). A pyridine ring has a higher reactivity than that of a benzene ring since quinoline selectively yields 3-borylquinoline (entry 10). Thus, borylation of pyridines gives β- or γ-coupling products depending upon steric or electronic effects of substituents, but it does not provide α-coupling products.



Scheme 2.11 Orientation of aromatic C–H borylation with $[Ir(OMe)(COD)]_2$·2dtbpy catalyst.

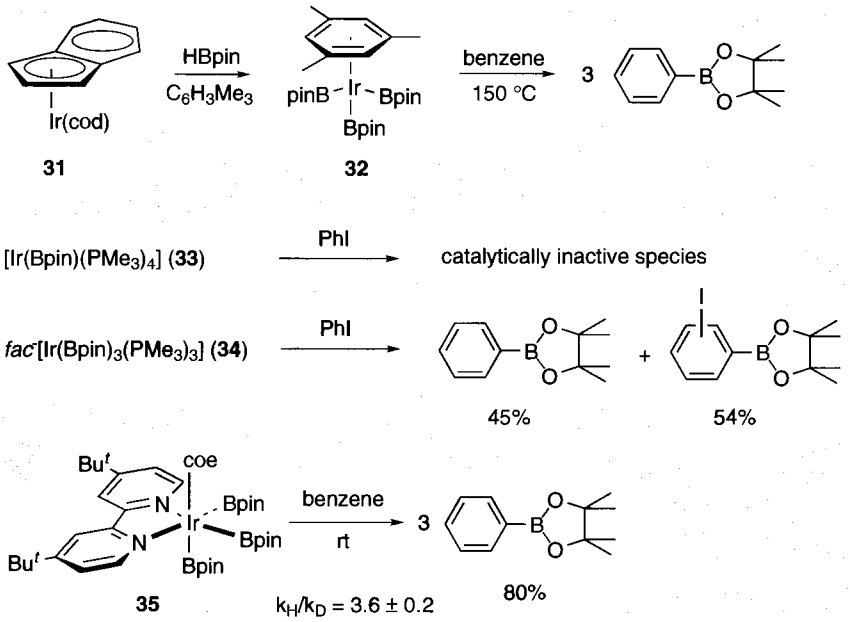
The ready availability of arylboronates by an aromatic C–H borylation provides a synthetic link to the well-established palladium-catalyzed cross-coupling reactions, rhodium-catalyzed 1,4-addition to α,β-unsaturated carbonyl compounds, and other bond forming reactions using arylboronic esters (Scheme 2.12). Borylation of 1,3-dichlorobenzene with pinacolborane is followed directly by a cross-coupling reaction with methyl *p*-bromobenzoate for the synthesis of a biaryl product in 91% yield [60]. Pinacol esters of arylboronic acids react much slower than the free acids [62], but both derivatives achieve high isolated yields and comparable enantioselectivities (91% ee) in asymmetric 1,4-addition to N-benzyl crotonamides [63]. Borylation of arenes followed by oxidation of the C–B bond is synthetically equivalent to an aromatic C–H oxidation to phenols [64]. Oxidation of the resulting arylboronates with Oxone in a 1:1 acetone–water solution is completed within 10 min at room temperature.



Scheme 2.12 Synthetic use of pinacol arylboronates.

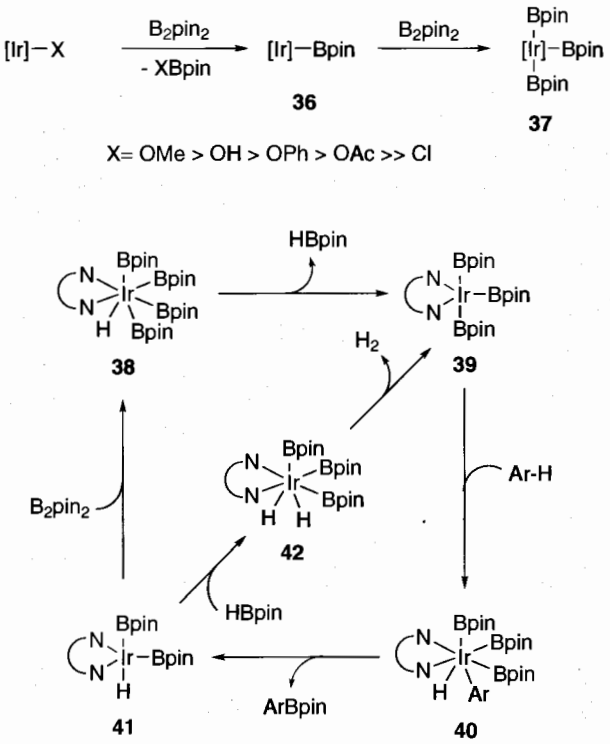
2.4.4 Catalytic Cycle

Interaction between Ir(η^5-C_9H_7)(cod) (**31**) and an excess of pinacolborane or catecholborane yields an arene-tris(boryl)iridium complex (**32**) [26], which reacts with benzene to produce three equivalents of PhBpin at 150 °C (Scheme 2.13). Although **32** itself is not effective for a catalytic reaction, addition of PMe_3 to **32** provides a species (**33** or **34**) effective for borylation of arenes with HBpin [57a]. Trimethylphosphine complexes (**33** and **34**) react cleanly with benzene to produce PhBpin and [Ir(H)$(PMe_3)_4$] or *fac*-[Ir(Bpin)$_2$(H)$(PMe_3)_3$] at room temperature, thus indicating that both iridium(I)- and iridium(III)-boryl species are viable for aromatic C–H borylation [57a]. However, there is a large difference in reactivity for iodobenzene between Ir(I) and Ir(III) complexes. The Ir(I)-boryl complex (**33**) does not yield coupling product whereas Ir(III)-tris(boryl) complex (**34**) affords two coupling products that are the same as that of catalytic borylation of iodobenzene. Mechanistic studies by Hartwig's group have also shown that the Ir(III)-tris(boryl) complex is an active component involved in the catalytic cycle [59a]. ^{1}H NMR spectroscopy for the reaction of B_2pin_2 in benzene at a high catalyst loading of ½[IrCl(COD)]$_2$/dtbpy shows the formation of a dtbpy-ligated tris(boryl)Ir(III) complex (**35**) that was finally isolated and characterized by X-ray analysis. When **35** is dissolved in benzene at room temperature, 3 equivalents of pinacol phenylboronate (80%) are produced instantaneously. Thus, iridium(III)-tris(boryl) complexes (**34** and **35**) are chemically and kinetically competent as intermediates in the catalytic process.



Scheme 2.13 tris(Boryl)Ir(III) intermediates involved in the catalytic cycle.

The reaction may proceed through a catalytic cycle analogous to that proposed for the Rh(I)-catalyzed borylation of alkanes [53] (Scheme 2.14). Thus, oxidative addition of an arene to a tris(boryl)Ir(III) intermediate (**39**) yields an Ir(V) species (**40**) that reductively eliminates ArBpin to give an Ir(III) hydride complex (**41**). Oxidative addition of B_2pin_2 to **41** can be followed by reductive elimination of HBpin to regenerate **39**. The resulting HBpin participates in the catalytic cycle via a sequence of oxidative addition to **41** and hydrogen reductive elimination from an 18-electron Ir(V) intermediate (**42**). Borylation of arenes with HBpin may occur after consumption of B_2pin_2, since the catalytic reaction shows a two-step process: fast borylation by B_2pin_2 followed by slow borylation by HBpin [59a]. Although catalytic cycles involving Ir(III)–Ir(V) intermediates are rare, the ease of elimination of HBpin or H_2 from an 18-electron Ir(V) intermediate (**38** and **42** respectively) without irradiation of light or a hydrogen-trapping reagent (e.g., alkenes) [65] should greatly contribute to such smooth borylation under mild conditions. A small steric hindrance from the planar bipyridine ligand as well as its electron donation to the metal center allows oxidative addition of an arene C–H bond, giving intermediate **40**. The small steric influence of the planar dioxaboryl rings (Bpin) and an arene substrate (Ar) can also be critical for the formation of such sterically hindered hepta-coordinated Ir(V) intermediates. These processes have been supported by recent theoretical studies by Sakaki [66].



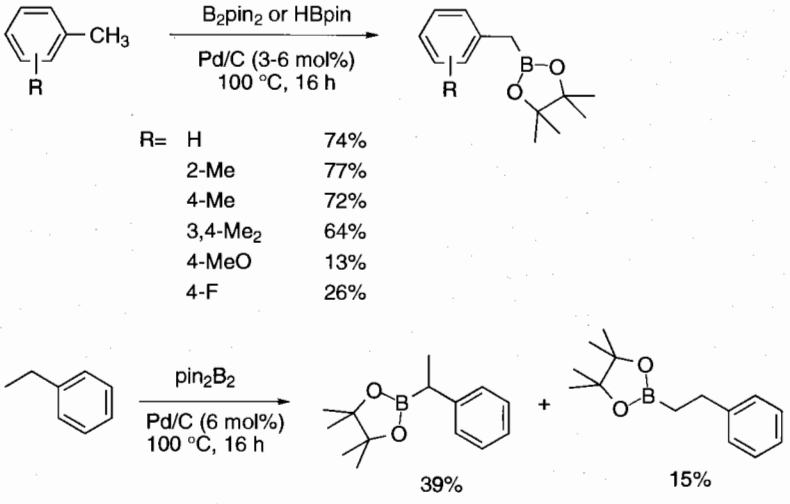
Scheme 2.14 Proposed catalytic cycle for aromatic C–H borylation.

A tris(boryl)Ir(III) intermediate (**37**) can be produced by oxidative addition of B_2pin_2 to a mono(boryl)Ir(I) complex (**36**). Thus, smooth formation of **36** from an Ir(I) source is critical for in situ generation of a reactive species via σ-bond metathesis between [Ir]-OMe and B_2pin_2, or by an oxidative addition–reductive elimination sequence. The (methoxo)iridium(I) complex $[Ir(OMe)(cod)]_2$ is a better precursor than $[Ir(Cl)(cod)]_2$, since it smoothly yields the mono(boryl) complex **36** at room temperature due to the higher bond energy of the resulting B–O bond than that of the B–Cl bond. Thus, the catalyst activity parallels the order of basic strength of the anionic ligand; X = MeO > HO > PhO > AcO ≫ Cl. An analogous effect of anionic ligands has been reported for transmetalation involved in palladium-catalyzed cross-coupling reactions of organoboron compounds [2, 32].

2.5
Benzylic C–H Borylation

Benzylic C–H borylation giving benzylboronates was first reported by Marder [58]. The reaction of HBpin in toluene in the presence of $RhCl\{P(i\text{-}Pr)_3\}_2(N_2)$ (1 mol%) at 140 °C gives (borylmethyl)benzene and {bis(boryl)methyl}benzene in 69% and 7% yields respectively, along with several products arising from aromatic C–H borylation (ca. 15%).

Pd/C is a unique catalyst for carrying out the selective benzylic C–H borylation of alkylbenzenes by B_2pin_2 or HBpin (Scheme 2.15) [67]. The reaction of B_2pin_2 in toluene proceeds at 100 °C to afford two equivalents of pinacol benzylboronate in 74% yield as the sole product. Xylenes and mesitylene are all viable substrates; however, the reaction can be strongly retarded by the presence of heteroatom functionalities such as MeO and F. Ethylbenzene resulted in a 3:1 mixture of pinacol benzylboron



Scheme 2.15 Benzylic C–H borylation.

and homobenzylboron derivatives. Formation of the latter product can be attributed to positional isomerization of (benzyl)Pd intermediates to (homobenzyl)Pd species via a β-hydride elimination–insertion process.

Acknowledgments

Aromatic C–H borylation catalyzed by Ir-bpy complexes was carried out as a joint project in collaboration with Professor Hartwig's group. We are greatly indebted to Professor John F. Hartwig and his co-workers for their contribution to the elucidation of the mechanism and for helpful discussions with him.

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3
Coupling Reactions of Areneboronic Acids or Esters with Aromatic Electrophiles

Akira Suzuki

3.1
Introduction

Recently, there have been many reports of applications of organoboronic acid derivatives in various fields. Especially, such compounds provide unique and useful synthetic methodologies. Carbon–carbon bond formation reactions are important processes in chemistry, as they constitute key steps in the building of more complex molecules from simple precursors. During the initial stage of our exploration of organic syntheses employing organoboron compounds and organic halides, we found that the cross-coupling reaction of vinyl boron derivatives with vinyl halides proceeds smoothly in the presence of a base and a catalytic amount of a palladium complex to give the expected conjugated alkadienes and alkenynes stereo- and regioselectively in excellent yields. Not only vinyl borane derivatives, but other types of organoboron compounds react with organic electrophiles under these reaction conditions. Thus, (sp^3)C–B compounds (alkylboron compounds) and (sp^2)C–B compounds (aryl- and alkenylboron derivatives) readily cross-couple with several organic electrophiles to produce coupled products selectively in high yields. Additionally, American and German chemists independently established the reactivity of (sp)C–B compounds (1-alkynylborane derivatives) with electrophiles under specific conditions to yield the corresponding coupled products. The present author has most recently published a book on the reaction [1a], which covers publications until 2000.

Recently, several synthetic applications using such cross-coupling reactions have become powerful tools for the construction of new organic compounds. Among these reactions, aromatic–aromatic (or heteroaromatic) couplings are used most frequently, because of their importance in pharmaceutical processes and polymer sciences.

In this chapter, only new advances reported between 2001 and 2003 on aromatic–aromatic, aromatic–heteroaromatic, and heteroaromatic–heteroaromatic coupling reactions will be discussed due to space limitations. Readers are also encouraged to

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refer to other reviews that also cover other types of substrates such as alkenylboronic acids [1b–d].

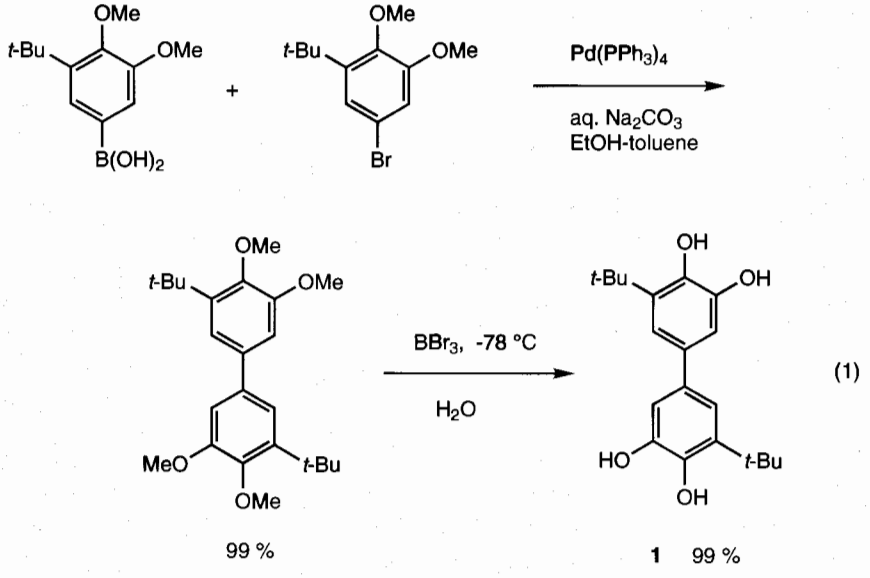
3.2
Coupling Reactions of Areneboronic Acid Derivatives

3.2.1
With Aryl Halides. Synthesis of Biaryls

The importance of biaryl units as components of many kinds of compounds, such as pharmaceuticals, herbicides, and natural products, as well as engineering materials such as conducting polymers, molecular wires, and liquid crystals, has attracted enormous interest from the chemical community. Palladium-catalyzed Suzuki coupling is the most important and efficient strategy for the construction of symmetrical and unsymmetrical biaryl compounds.

3.2.1.1 Aromatic–Aromatic Coupling

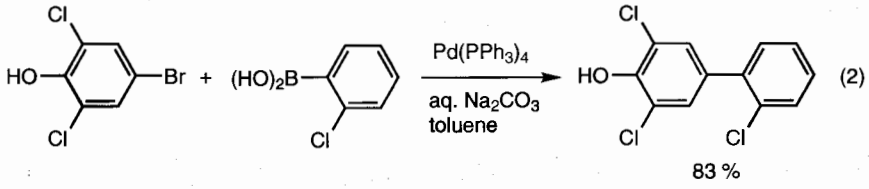
To study the charge distribution in bis-dioxolene radical metal complexes, the biphenyl **1** was synthesized by Suzuki coupling (Equation 1) [2].



(1)

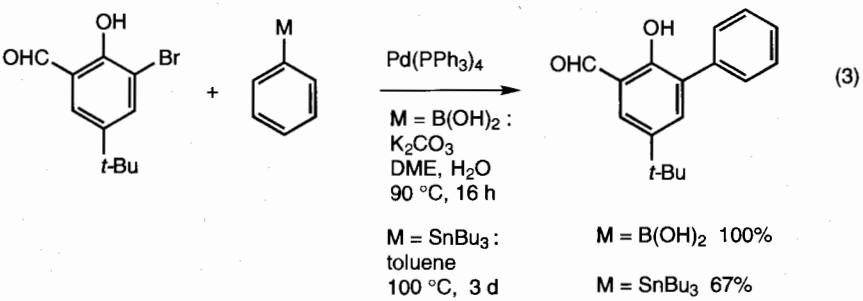
An important synthesis of hydroxylated polychlorinated biphenyls (PCBs), which are structurally related to the major hydroxy PCB congeners identified in human plasma, was reported. Coupling of chlorinated aryl boronic acids with chloro anisoles using the standard conditions of the Suzuki coupling gave hydroxylated PCB metabolites in good to excellent yields. The approach offers the advantages of high selectivi-

ty and good yields compared to conventional methods such as the Cadogan reaction, and allows the use of less toxic starting materials (Equation 2) [3].



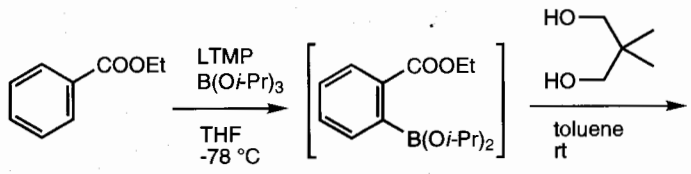
(2)

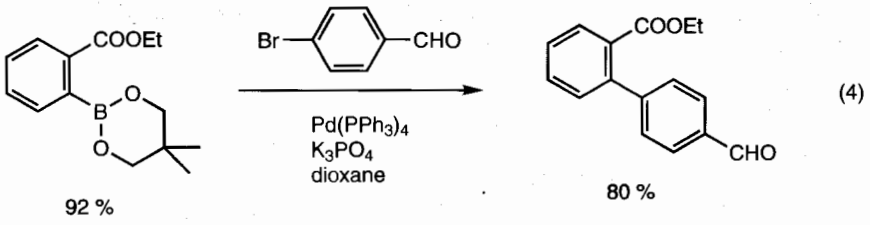
An efficient method for the preparation of 3-arylsalicylaldehydes by palladium-catalyzed cross-coupling reaction of arylboronic acids and 3-bromo-5-*tert*-butylsalicylaldehyde has been reported. Although Stille coupling also gave the similar coupled product, such a reaction required prolonged heating at high temperature and gave a relatively low product yield (Equation 3) [4].



(3)

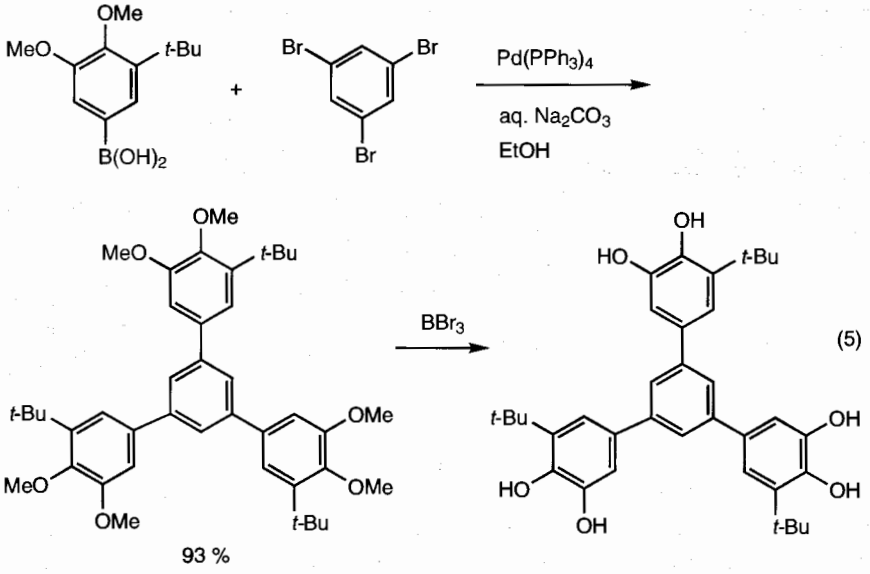
Ortho lithiation – in-situ boration using lithium 2,2,6,6-tetramethylpiperidide (LTMP) in combination with triisopropylborate is a highly efficient and experimentally straightforward process for the preparation of ortho substituted arylboronic esters. The mild reaction conditions allow the presence of functionalities such as ester, cyano groups, and halogen substituents that are usually not compatible with the conditions used in directed ortho-metalation of arene. Arylboronic esters prepared by ortho-metalation underwent Suzuki coupling reaction with a range of aryl halides, furnishing biaryls in good to excellent yields (Equation 4) [5].





(4)

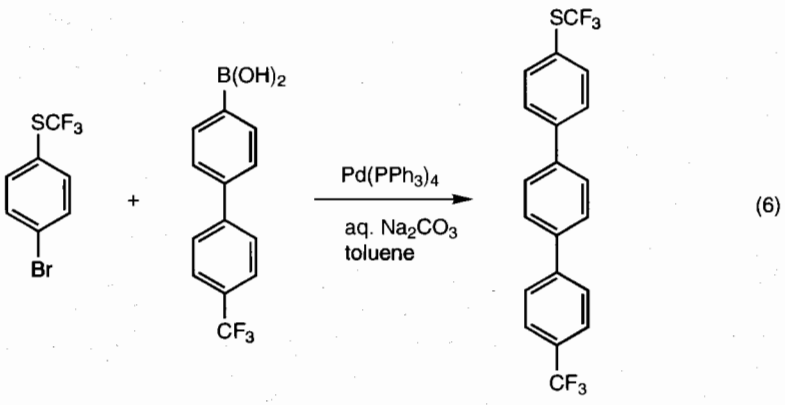
The tris-bidentate ligand 1,3,5-tris(5-*tert*-butyl-3,4-dihydroxyphenyl)benzene was synthesized by Suzuki coupling in an excellent yield, which affords high-spin metal complexes containing a ferromagnetically coupled tris(semiquinone) ligand (Equation 5) [6].



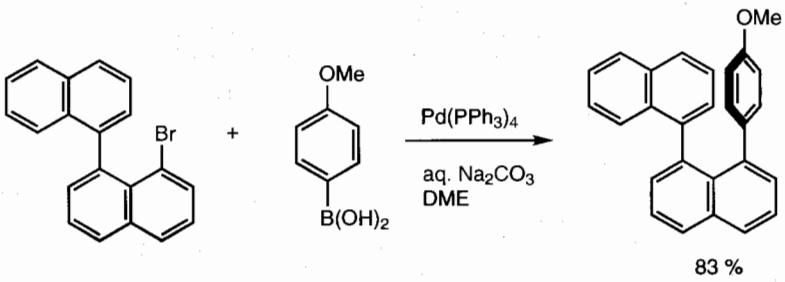
(5)

With ^{13}C-labeled samples, internuclear distances of up to 7 Å can be measured by solid-state NMR, thus providing a powerful tool for probing ligand–receptor interactions. However, limitations in measurable distances, and appreciable background signal due to naturally occurring ^{13}C, present problems in solid-state ^{13}C NMR. To overcome these disadvantages, a set of reference compounds with known F–F distances, namely, quinolinol, *p*-biphenyl, and *p*-terphenyl-bearing trifluoromethyl and trifluoromethylthio groups, have been synthesized by Suzuki coupling (Equation 6) [7].

1,8-Diaryl cofacial naphthalenes as well as cyclophanes continue to be useful model compounds to study the interactions between aromatic rings held near or below van der Waals interatomic distance. In such naphthalenes, the two aromatic rings are held cofacial but are splayed from each other and can rotate about the bonds attaching them to the rigid naphthalene frame, thereby giving rise to atropisomers. Such 1,8-diaryl naphthalenes were prepared by Suzuki coupling (Equation 7) [8].

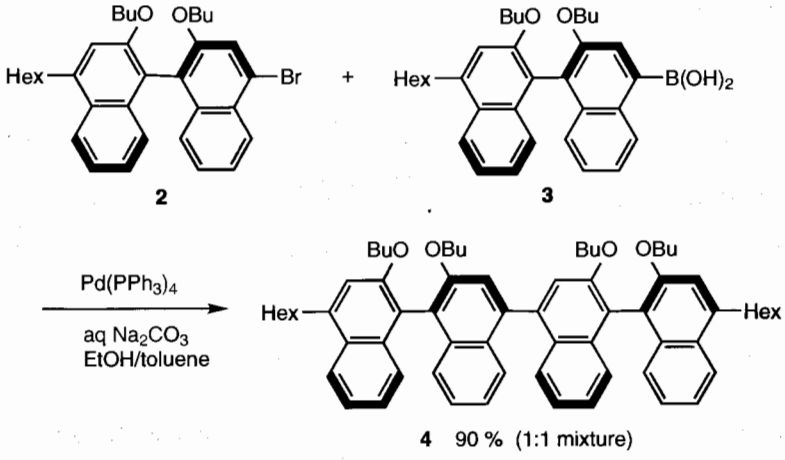


(6)



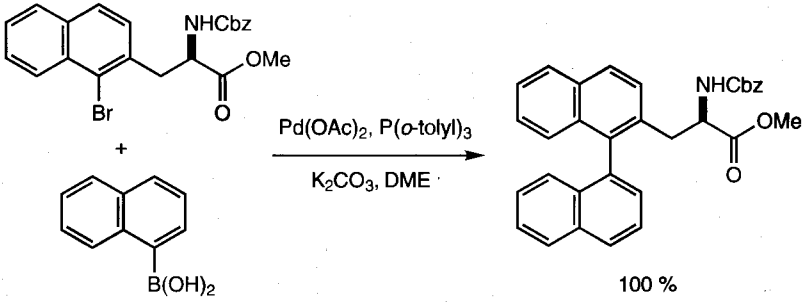
(7)

Suzuki coupling of optically active (*S*)-binaphthyl bromide **2** with (*S*)-binaphthylboronic acid **3** produced a diastereomeric mixture (1:1 mixture) of tetrabutoxyquaternaphthyl **4**. The C-1 and C-1' axis of the compound has an unusually high rotational barrier (Equation 8) [9].



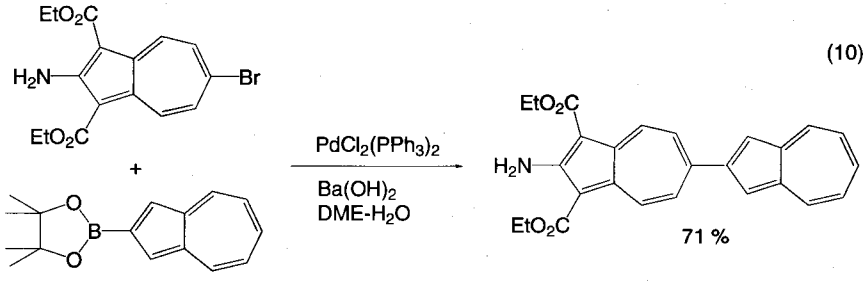
(8)

A series of novel hydrophobic, bulky χ^2-constrained phenylalanine and naphthylalanine derivatives were designed and synthesized by Suzuki coupling of α-amino acid derivatives with boronic acids to afford these aromatic substituted amino acids in high yields and with high enantioselectivity (Equation 9) [10].

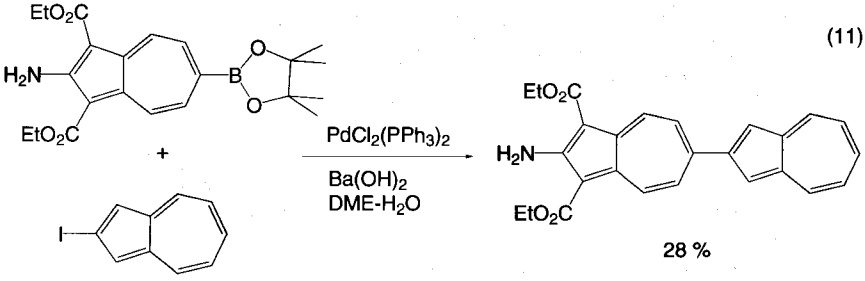


(9)

Azulene oligomers and polymers are intriguing molecules in terms of the construction of functional substances. Some synthetic studies on azulene dimers have been reported. The synthetic methods, however, were considered to restrict the development of further studies. Thus, Ullman coupling reactions at high temperature or some sophisticated reactions based on Hafner's azulene synthesis, starting from bipyridyls, were used. To obtain azulene oligomers, the Suzuki coupling has been applied recently (Equations 10 and 11) [11].

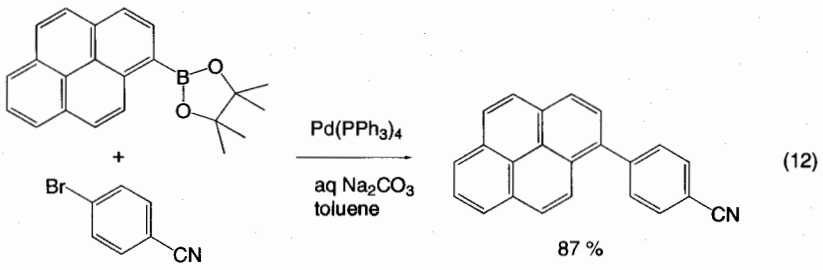


(10)



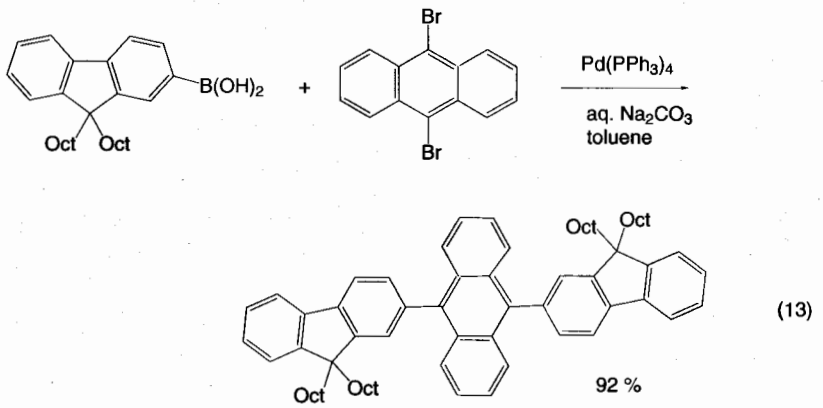
(11)

Various substituted phenyl pyrenes, synthesized by Suzuki coupling, have been investigated by fluorescence spectroscopy (Equation 12) [12].



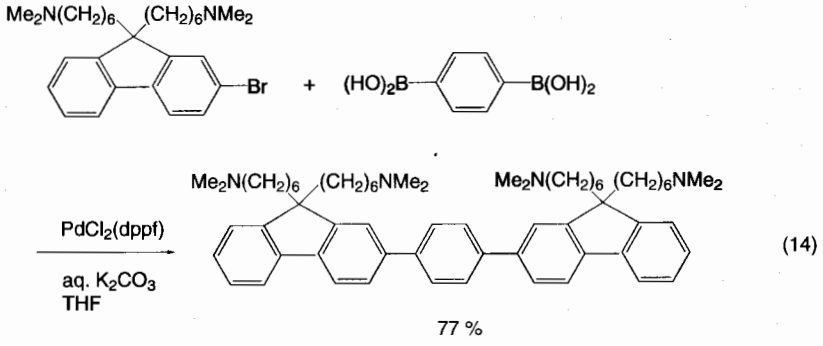
(12)

A new example of magnetic non-equivalence of chemically equivalent atoms was identified from the proton and carbon resonance spectra of 9,10-di(9,9-dioctylfluorenyl)anthracene with the aid of its conformation in the crystalline state. The desired compound was synthesized by a Suzuki reaction (Equation 13) [13].



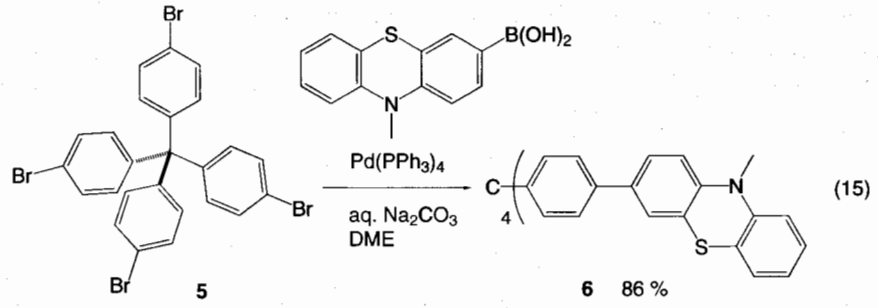
(13)

Water-soluble conjugated polymers are of particular interest in biosensor schemes. To compensate for the hydrophobic nature of the backbone, these polymers contain charged groups for solubility in aqueous media. As one of many syntheses of such oligomers, Suzuki coupling has been applied (Equation 14) [14].



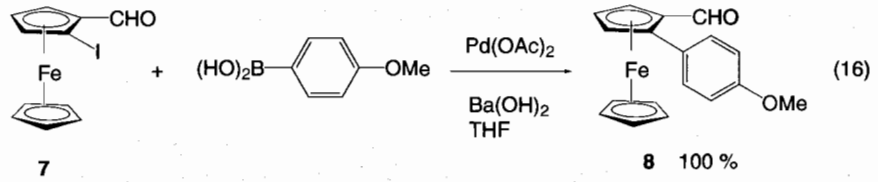
(14)

The novel class of tetrakis(phenothiazinylphenyl)methane **6**, showing remarkably large Stokes shift and a reversible low oxidation potential, can be prepared in good yield by Suzuki coupling of tetrakis(*p*-bromophenyl)methane 5, (Equation 15) [15].



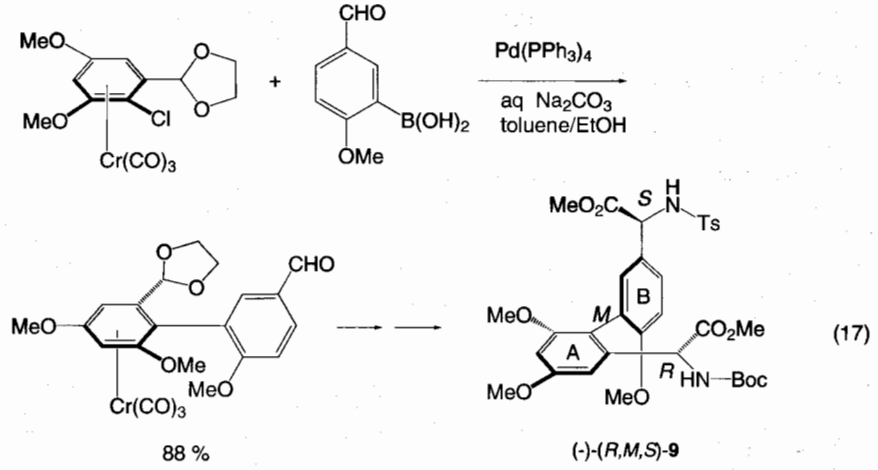
(15)

Palladium-catalyzed Suzuki coupling of the iodide (*S*)-**7** with areneboronic acids using the phosphine-free procedure gave aryl aldehydes, such as **8**, in excellent yields when barium hydroxide was used as the base (Equation 16) [16].



(16)

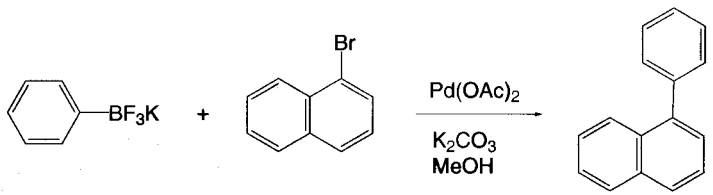
Asymmetric synthesis of a fully protected *ent*-actinoidinic acid derivative (**9**) was reported using a diastereoselective Suzuki coupling as the key step (Equation 17) [17].



(17)

The ligandless palladium-catalyzed Suzuki coupling reaction of potassium aryl- and heteroaryltrifluoroborates with aryl- or heteroaryl halides or triflates proceeds readily with very good yields. Cross coupling can be effected in methanol or water, using $Pd(OAc)_2$ as a catalyst in the presence of K_2CO_3. Various functional groups are

tolerated. Moreover, under these conditions, the reactions could be performed in air without any effect on the high yield of biaryls (Equation 18) [18].



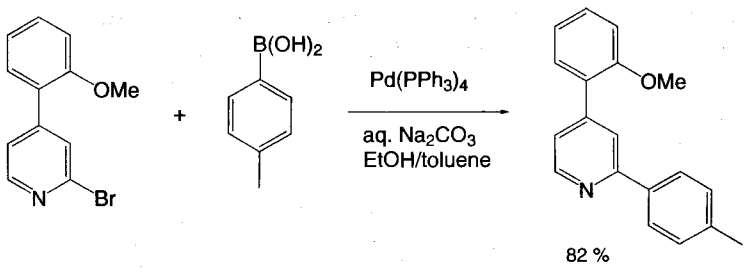
88 %

(18)

The variant of the reaction using trifluoroborate salts, gives very good results when performed in refluxing methanol. Previous reports have indicated that water was required as a co-solvent for the trifluoroborate coupling reactions [19, 20], and that one or more hydroxy groups displace fluorides on the tetracoordinate boron species involved in the transmetallation step of the catalytic cycle [20–22]. Molander and Ito have conducted experiments by heating $PhBF_3K$ in methanol at reflux, with the addition of 0, 1, 2, and 3 equiv of base. After 2 h, all reaction mixtures were filtered, and equal amounts of deuterated acetone were added to each one; the resulting solutions were then analyzed using ^{11}B and ^{19}F NMR spectroscopy. The ^{19}F NMR spectra showed the absence of fluorine bonded to the boron atom after adding 3 equiv. of base. ^{11}B NMR shifts revealed a quadruplet at 4.35 ppm when no base was added and a singlet at 5.47 ppm when 3 equiv of base was added. Molander and Ito thus concluded that the trifluoroborates do not remain intact under the reaction conditions and that an intermediate that does not retain all of the fluorides on the boron species is involved in the key transmetallation step [19]. Using a different analysis, Batey and Quach previously came to the same conclusion [20]. These results strongly support the mechanism of palladium-catalyzed coupling of organoboranes proposed by Suzuki and co-workers [22]. From mechanistic studies of Suzuki reactions [22], it is likely that the boron reagent first reacts with the base to give the corresponding boronate, which serves as the actual nucleophile. It then transfers the organic ligand to the hydroxypalladium(II) complex formed by insertion of the Pd(0) into the C–X bond followed by the displacement of X with the hydroxide ion. In this system the aqueous layer contains the base, and the organic phase contains the aryl halide. The palladium catalyst and the boronate salt are partitioned between aqueous and organic phases.

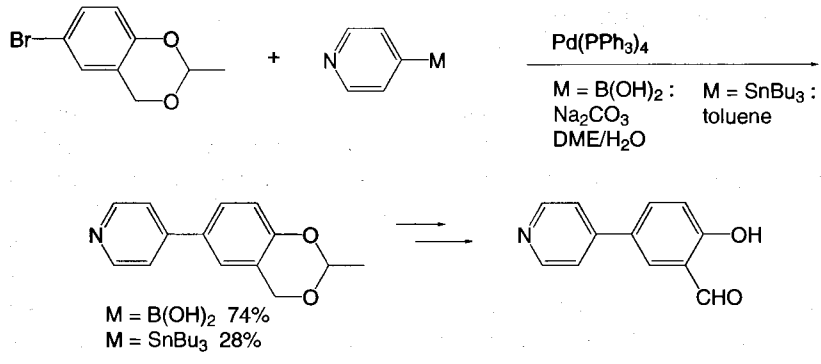
3.2.1.2 Aromatic–Heteroaromatic and Heteroaromatic–Heteroaromatic Couplings

Pd-mediated Suzuki coupling reactions provide a flexible entry to substituted pyridines (Equation 19) [23].



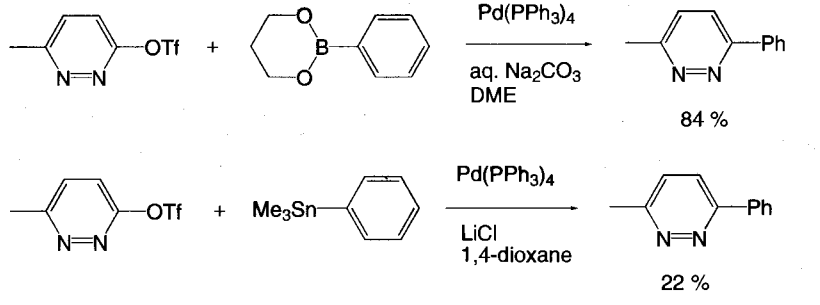
(19)

An efficient method for the preparation of 5-(3-pyridyl)- and 5-(4-pyridyl)-salicylaldehydes by the Suzuki coupling reaction of either 4-pyridylboronic acid or diethyl-(3-pyridyl)borane and bromosalicylaldehydes was reported. While Suzuki coupling gives high product yields (Equation 19), Stille coupling using pyridylstannane derivatives provides poor yields (Equation 20) [24].



(20)

Similarly, the scope of trifluoromethanesulfonic acid 6-methyl-pyridazine-3-yl ester as a coupling partner for biaryl synthesis via palladium catalyzed Suzuki and Stille coupling conditions has been reported (Equations 21 and 22) [25].

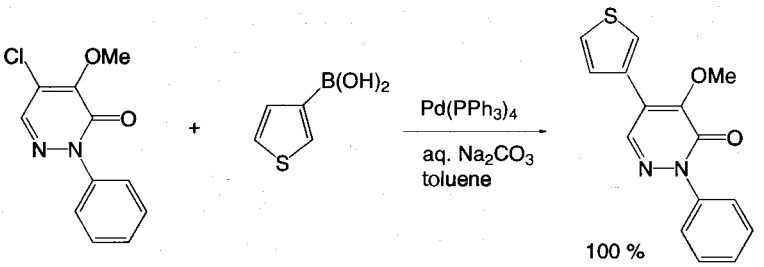


(21)

(22)

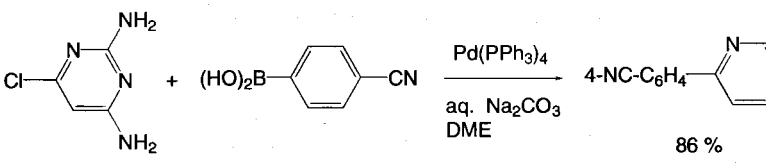
2,4,5-Trisubstituted-3(2*H*)-pyridazinones are well known in agrochemical and pharmaceutical research. One of the oldest is Chloridazon [5-amino-4-chloro-2-phenyl-3(2*H*)-pyridazinone]. This commercial herbicide, developed by BASF researchers, is still extensively used for weed control in sugar beet and red table beet

cultivation. Since the marketing of Chloridazon, many patents and papers has been published dealing with the synthesis and pesticidal activity of 2,4,5-trisubstituted-3(2*H*)-pyridazinones. Besides their agrochemical applications, several interesting pharmaceutical activities have been reported (e.g. analgesic, antiinflammatory, anticonvulsant, antitumor, antiviral, antibacterial, and antifungal). Consequently, the new and convenient synthesis of 4-aryl-5-methoxy-, 5-aryl-4-methoxy-, and 4,5-diaryl-3(2*H*)-pyridazinones via Suzuki coupling reactions with the corresponding chloro-3(2*H*)-pyridazinones has been reported recently; an example is depicted in Equation 23 [26].



(23)

Despite potentially interesting molecular recognition, agrochemical and medicinal properties, the syntheses of 6-aryl-2,4-diaminopyrimidines and triazines are largely unexplored. Recently, Cooke et al. have described the high yielding synthesis of such compounds via palladium-catalyzed Suzuki coupling reactions of commercially available 6-chroro-2,4-diaminopyrimidine (**10**) or 6-chloro-2,4-diaminotriazine (**11**) and aryl boronic acids (Equations 24 and 25) [27].



(24)

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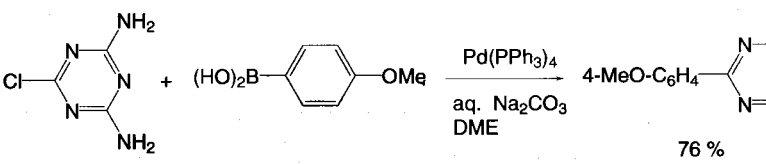

(25)

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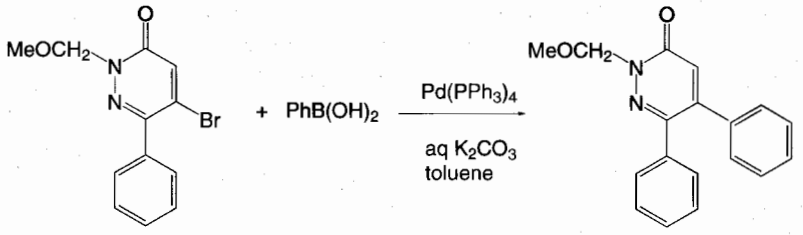
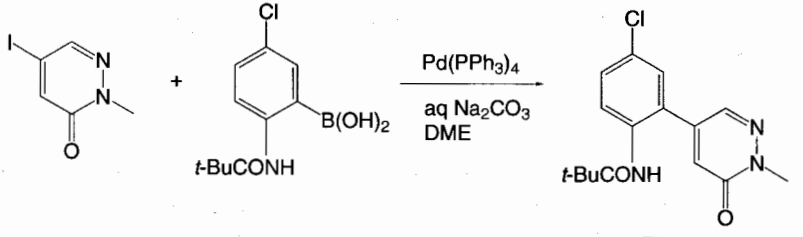
A highly efficient procedure for introducing aryl or heteroaryl rings at position 5 of the 6-phenyl-(2*H*)-pyridazin-3-one system using a Suzuki coupling reaction has been developed in the search for new platelet aggregation inhibitors (Equation 26) [28].



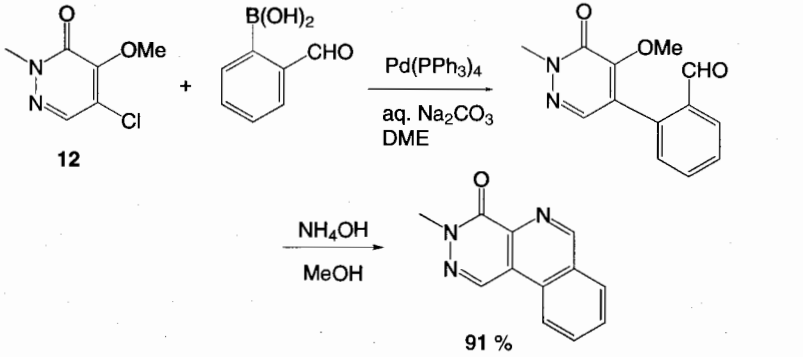
98 % (26)

5-Iodo-2-methylpyridazin-3(2*H*)-one readily undergoes Suzuki coupling with protected anilinoboronic acids to yield the corresponding arylpyridazinones, which proved to be suitable starting compounds to a ring closure – a four-step pathway – to pyridazino[4,5-*b*]indoles (Equation 27) [29].

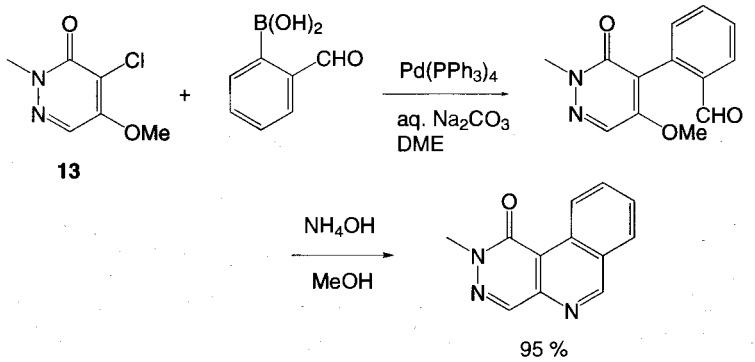


79 % (27)

Suzuki coupling reactions of **12** and **13** with 2-formylphenylboronic acid afforded the corresponding biaryl products, which were cyclized with ammonia to yield hitherto undescribed pyridazino[4,5-*c*]isoquinolinones (Equations 28 and 29) [30].

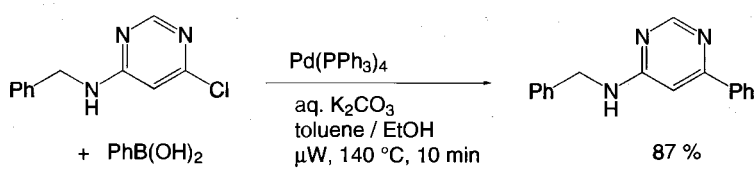


91 % (28)



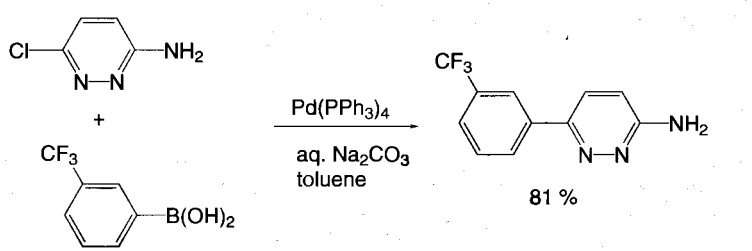
(29)

Substituted amino pyrimidine structures are common in many marketed drugs and other medicinally relevant compounds. Conventional syntheses include ring formation reactions and thermal nucleophilic aromatic substitution reactions of amines with halogenated pyrimidines. Nucleophilic aromatic substitution reactions of electron deficient halogenated pyrimidines are usually rapid and high yielding. However, with electron-rich or even neutral halogenated pyrimidines (ca. with alkyl, alkoxy or amino substituents) the substitution reactions require prolonged heating for hours or days. Only one report on the synthesis of C-aryl pyrimidines with halogenated pyrimidines through Suzuki coupling was made before [31]. The reaction under conventional heating takes many hours to days and no amino-substituted halopyrimidines were reported. Most recently, Luo et al. have reported that the microwave-assisted Suzuki coupling reaction of halogenated aminopyrimidines generally achieves complete conversion within 15 min to give coupled products in high yield (Equation 30) [32].



(30)

Although many pyridazines are biologically active and the whole family of pyridazine derivatives shows a broad diversity of biological activities, useful for pharmaceutical and agrochemical applications, the Suzuki coupling reaction in pyridazine chemistry was not systematically studied. Recently, Lemiere et al. have reported such reactions on chloropyridazines (Equations 31 and 32) [33].



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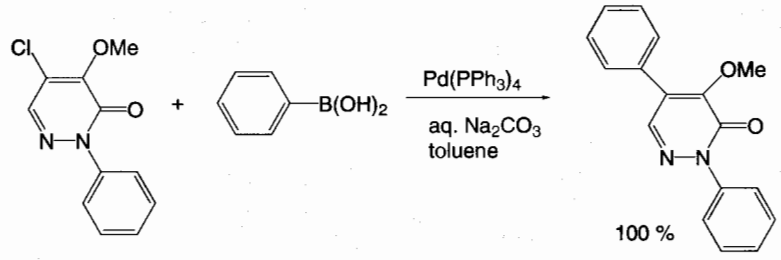
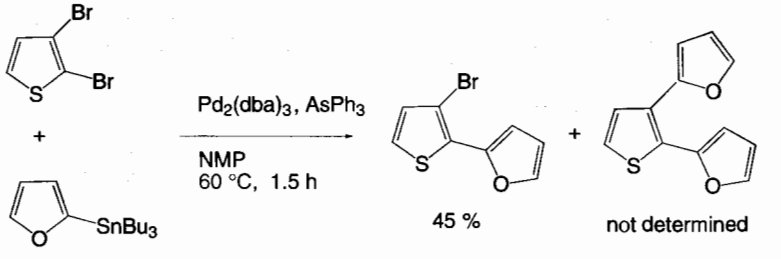
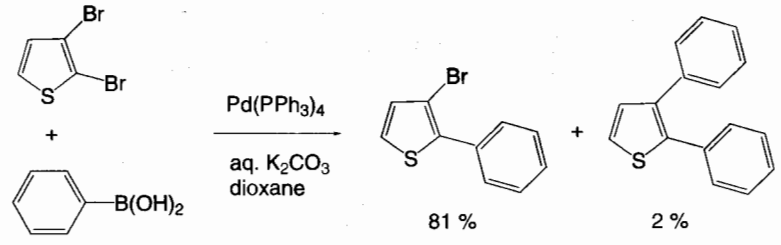


(32)

Recently, de Lera et al. have carried out regioselective palladium-catalyzed cross-coupling reactions, Suzuki coupling and Stille coupling, in the synthesis of novel 2,3-disubstituted thiophene derivatives. They reported that regioselective coupling at C2 could be accomplished efficiently by Suzuki coupling under similar conditions (Equations 33 and 34) [34].

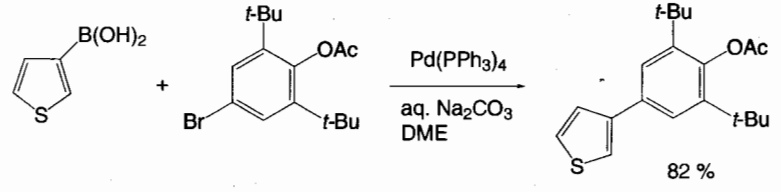


(33)



(34)

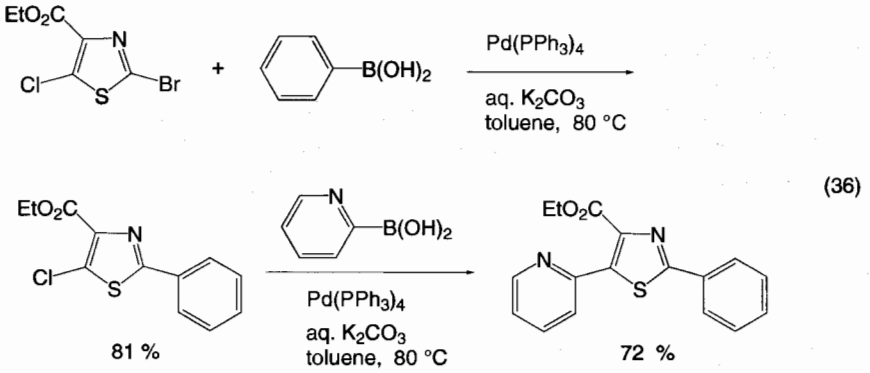
For a synthesis of a new high-spin organic polymer, Nishide et al. produced 3-(3′,5′-*tert*-butyl-4-acetoxyphenyl)thiophene by a Suzuki reaction (Equation 35) [35].



(35)

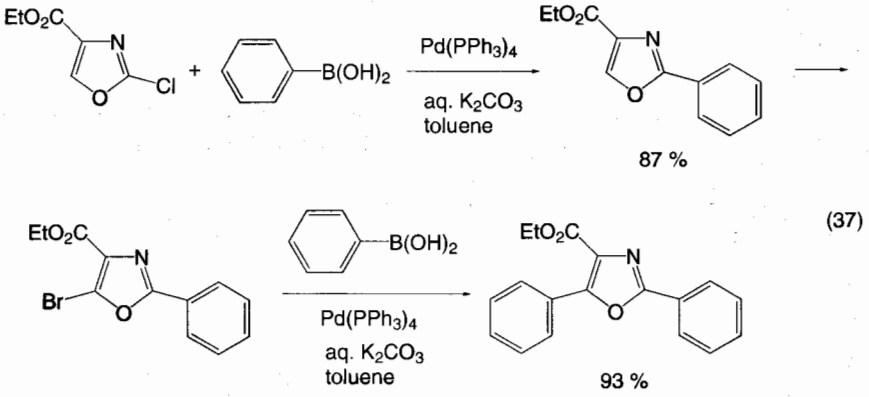
Thiazoles occupy a prominent position among heterocycles. Many of them obtained from microbial and marine origins exhibit important biological effects such as antitumor, antifungal, antibiotic, and antiviral activities. Synthetic thiazoles exhib-

it a wide variety of biological activity, while others have found application as liquid crystals and cosmetic sunscreens. The classical method for the synthesis of thiazoles is the Hantzsch process, in which an α-haloketone is condensed with a thioamide. This method gives excellent yields for simple thiazoles; however, for some substituted examples low yields have been reported as a result of dehalogenation of the α-haloketone during the reaction. Hodgetts and Kershaw have reported recently the regiocontrolled synthesis of 2,5-disubstituted and 2,4,5-trisubstituted thiazoles from ethyl 2-bromo-5-chloro-4-thiazolecarboxylate using sequential Suzuki coupling reactions (Equation 36) [36].



(36)

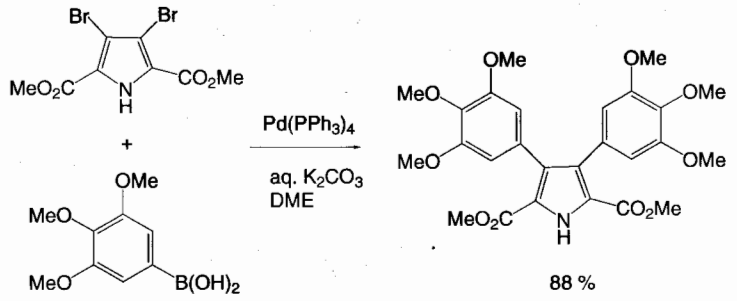
By using a sequence of regiocontrolled halogenation and palladium-catalyzed coupling reactions, the synthesis of variously substituted oxazoles from 2-chlorooxazole-4-carboxylate was accomplished. The methodology was applied to the synthesis of a series of 2,4-disubstituted, 2,5-disubstituted, and 2,4,5-trisubstituted oxazoles (Equation 37) [37].



(37)

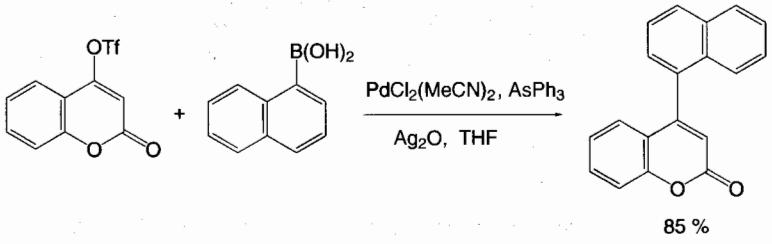
Palladium-catalyzed Suzuki coupling was used to convert the now readily available 3,4-dibromopyrrole derivative into the core structures of different pyrrole alkaloids.

Several compounds of this series exhibit respectable cytotoxicity and resensitized multidrug resistant cancer cell lines at non-toxic concentrations (Equation 38) [38].



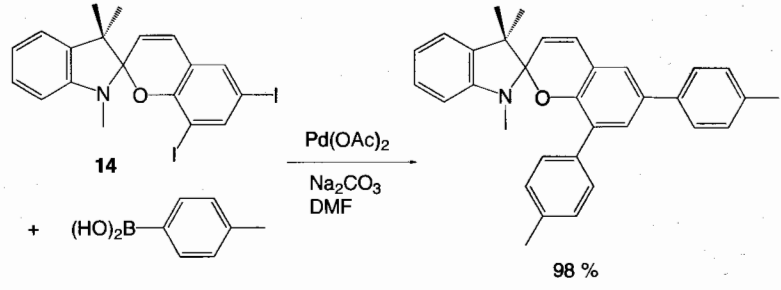
(38)

Palladium-catalyzed cross-coupling reaction of aryl-, alkenyl-, and cyclopropylboronic acids with 4-trifluoromethanesulfonyloxycoumarin provides the corresponding 4-substituted coumarins in 63–85% yields (Equation 39) [39].



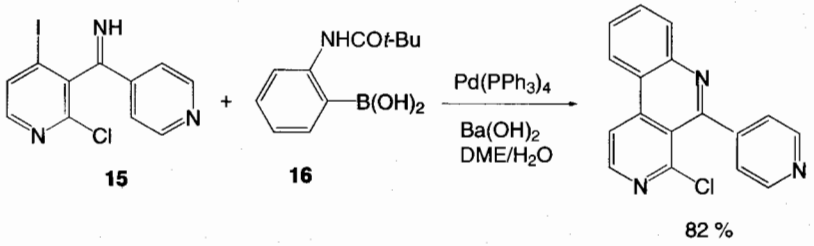
(39)

Photochromic indolinobenzopyran dyes have been paid considerable attention due to their potential application in many new technologies, including the area of rewritable optical memory and optical switching, nonlinear optics, and real-time holography. Because of the stability of the spiropyran structure, the absorption associated with the merocyanine chromophore and other physical properties are strongly dependent on the substituent. It is therefore of interest and important to investigate the influence of structural changes to the parent spiropyran, especially for a ferroelectric liquid crystal optical switch based on the principle of photoresolution. Consequently, 6-iodospiropyrans and 6,8-diiodospiropyran **14** were coupled with arylboronic acids in the presence of palladium acetate and sodium carbonate in DMF to give the corresponding spiropyrans in high yields (Equation 40) [40].



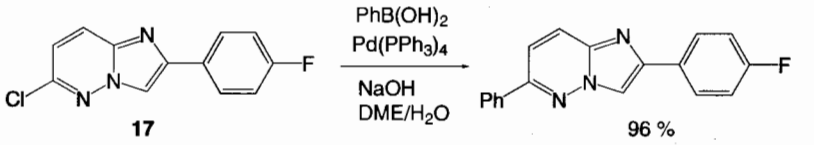
(40)

Suzuki coupling reactions provide a very efficient and fruitful strategy to polycyclic molecules of biological interest. For example, imine **15** reacts with phenylboronic acid **16** under Suzuki's conditions. Spontaneous cyclization of the intermediate phenylpyridine leads to the expected 4-chloro-5-(4-pyridyl)benzo[*c*]-2,7-naphthyridine in 82% yield (Equation 41) [41].



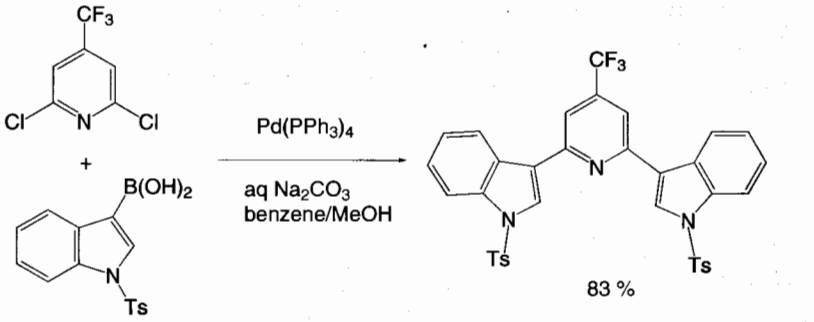
(41)

Generally, in Suzuki coupling, chloroarenes are less suitable. Nevertheless, Suzuki reactions have been described on chloropyridines [42], chloropyrimidines [43], chloropyrazines [43], chloropyridazines [44], chlorotriazines, [45], chloroquinoline [42, 46], chloroisoquinoline [47], chloropurines [48], chlorothiophene [46, 49], chlorocoumarine [46], chlorocinnoline [50], chloroquinazoline [50], chloropyrrolopyrimidine [45], chloropyrazolopyrimidine [45], and chlorotriazolopyrimidine [45]. Additionally, Enguehard et al. have reported recently a Suzuki coupling of 4-chloroimidazo[1,2-*b*]pyridazine derivatives **17** (Equation 42) [51].



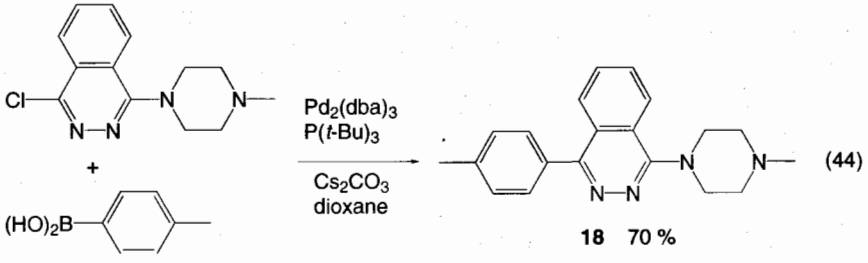
(42)

Bis(indolyl)-4-trifluoromethylpyridine has been synthesized using Suzuki coupling between 2,6-dichloro-4-trifluoromethylpyridine and *N*-tosyl-3-indolylboronic acid. This compound was evaluated for cytotoxic activity against P388 (Equation 43) [52].



(43)

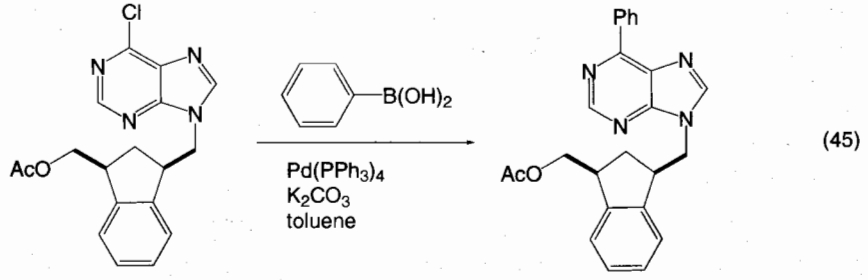
Rival et al. have reported the application of the Suzuki reaction to 4-chloro-1-(4-methylpiperazin-1-yl)phthalazine, examining the scope and the various reaction conditions. This new route represents a faster, two-step access to the unsymmetrical 1,4-disubstituted phthalazines **18**. The best results using this reaction were obtained with electron-donating substituents such as OMe and Me (Equation 44) [53].



18 70 %

(44)

Purine bases and their nucleosides constitute an important class of antineoplastic and antileukemic agents. Efforts to improve their efficiency in these roles have resulted in the introduction of various structural modifications in both the base and the sugar moiety. Recently, Suzuki reactions of the 6-chloropurine derivative **19** with phenylboronic acids was reported to afford **20** (Equation 45) [54].

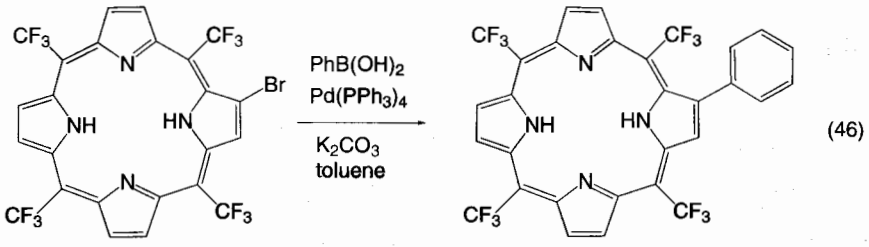


19

20 73 %

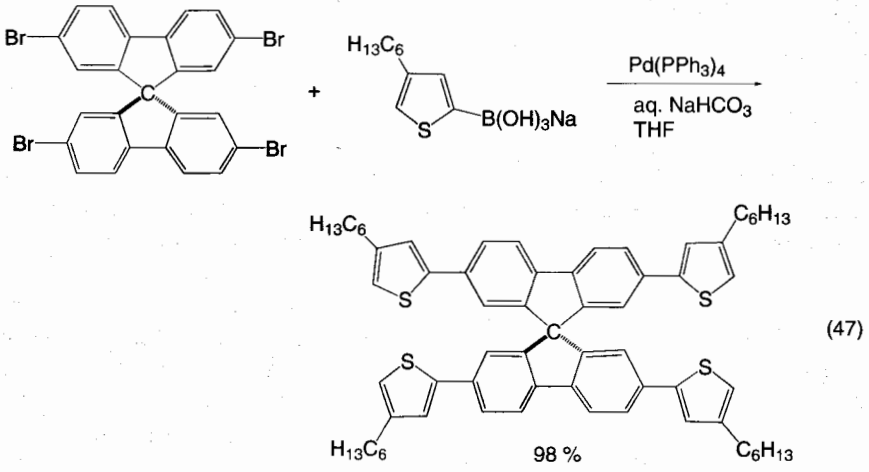
(45)

Porphyrins and metalloporphyrins are actively pursued in organic, material, bioinorganic, and organometallic chemistry. Electron-withdrawing porphyrins have emerged as an important subclass, especially for their oxidative robustness as ligands for metalloporphyrin oxidation catalysts. Among the electron-withdrawing groups, the trifluoromethyl group is an ideal substituent since it possesses additional lipophilic property. Recently, free base β-bromoporphyrins such as **21** were converted into aryl porphyrins through Suzuki coupling (Equation 46) [55].



21 98 % (46)

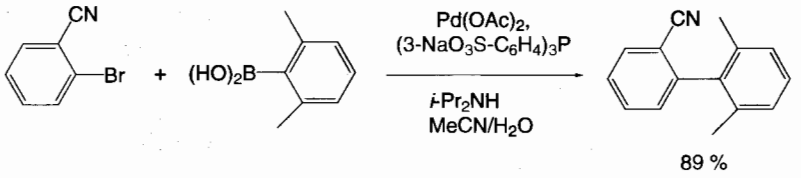
Oligothiophene functionalized 9,9′-spirobifluorene derivatives have been synthesized by Suzuki coupling in high yields. The Negishi coupling reaction between oligothienylzinc chloride and various 9,9′-spirobifluorene bromides with $Pd(PPh_3)_4$ as catalyst successfully produces the desired compounds. However, the Negishi coupling provided a low yield compared to the Suzuki coupling (Equation 47) [56].



(47)

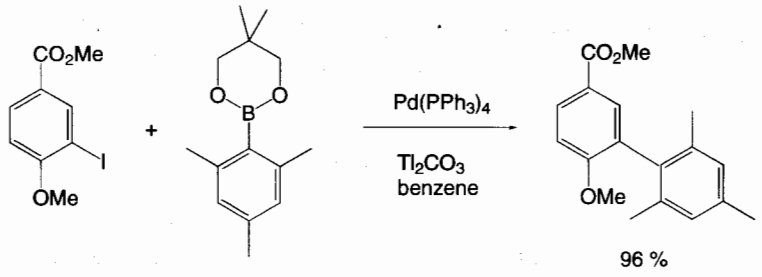
3.2.1.3 Coupling of Sterically Hindered Arylboronic Acids or ones Possessing Electron-attracting Substituents

Genet et al. have reported recently that Suzuki cross-coupling reactions between a range of aryl bromides and boronic acids using a water-soluble Pd/TPPTS (sodium triphenylphosphinometatrisulfonate) catalyst occur under mild conditions with high efficiency. The process tolerates both electron-rich and electron-poor substituents and provides an efficient access to sterically hindered biaryls. Good turnovers are observed and the catalyst can be recycled three times without loss of activity (Equation 48) [57].



(48)

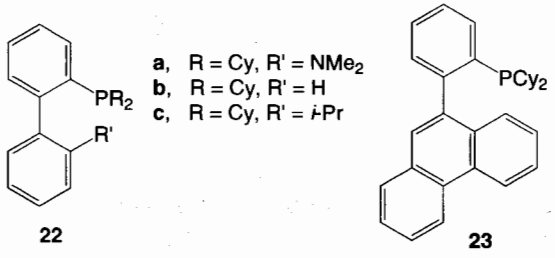
3-Iodo-4-methoxybenzoic acid methyl ester has been cross coupled with sterically hindered arylboronic esters in a process that was optimized to obtain biaryls in good yields (e.g. Equation 49) [58].

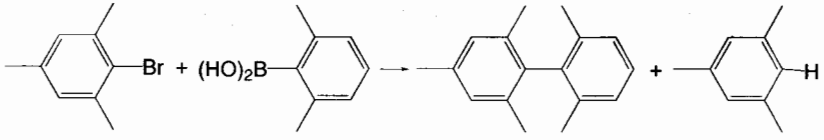


(49)

As part of the studies of Buchwald's group on the Suzuki coupling, they reported a general catalyst to prepare tetra-ortho-substituted unsymmetrical biaryls [59]. They also reported new ligands for such processes and crystallographic evidence for an unusual π-coordination mode [60]. In initial studies with biphenyl-based ligands **22a-c**, significant amounts of aryl bromide reduction were observed (Table 3.1) [61].

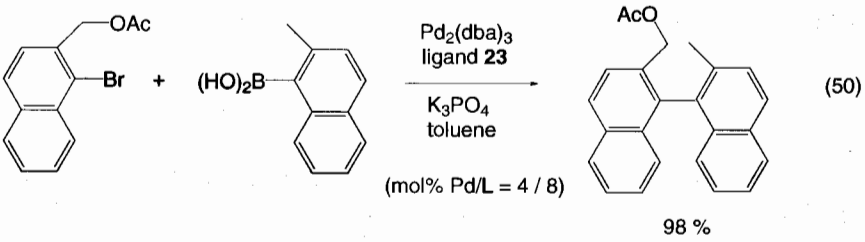
Table 3.1 Ligand effects in the coupling of hindered substrates.





Ligand	Conv (%)	Biaryl (%)	Biaryl/Ar-H
22a	47	33	2.3
22b	20	10	0.9
22c	74	40	1.9
23	100	91	10

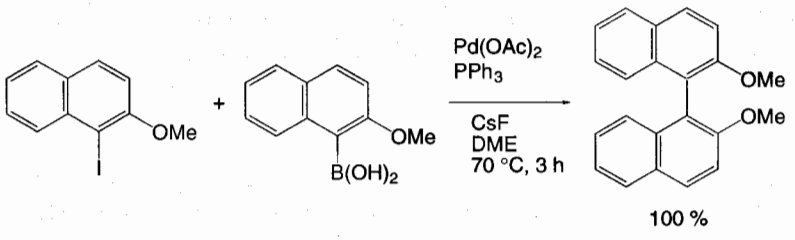
Phosphine **23** proved in general to be an excellent ligand for Suzuki coupling reactions to form sterically hindered tetra-ortho-substituted biaryls in good yields. Ortho substituents such as methyl, primary alkyl, phenyl, and alkoxy groups are accommodated. It was necessary to use 2.0 equiv of the boronic acid to effect complete consumption of the aryl bromide in some cases, presumably due to competitive protodeboronation. Crystallographic analysis of **23**/Pd(dba) revealed an unusual π-coordination of the phenanthrene moiety – the first of its type for a Pd(0) complex (Equation 50) [61].



(50)

To obtain configurationally stable chiral biaryls, at least three ortho substituents are usually necessary. The usual Suzuki coupling procedure using $Pd(PPh_3)_4$ and aqueous Na_2CO_3 in DME or benzene at 80 °C works effectively for most arylboronic acids. However, arylboronic acids that are either sterically hindered or have electron-withdrawing substituents never provide satisfactory results under these conditions due to steric hindrance or competitive hydrolytic deboronation. Furthermore, to obtain acceptable yields of hindered biaryls, high temperatures (80–110 °C) are usually needed with multihour reaction times. In atropisomer selective reactions, these conditions would be deleterious to the discrimination between diastereomeric transition states and could also racemize the biaryls formed. Consequently, sterically hindered biaryl coupling has attracted considerable recent attention. Investigations at various temperatures and with different bases were developed and it was pointed out that addition of stronger bases than Na_2CO_3, e.g. aqueous NaOH or $Ba(OH)_2$, exerts a remarkable effect on accelerating the rate of coupling [62]. Moreover, Anderson demonstrated that certain hindered biaryls can be formed in good yields via Suzuki coupling at room temperature with thallium(I) hydroxide in DME [63]. Subsequently, sodium phenoxide and silver carbonate at reflux in benzene proved to be a useful alternative to the toxic thallium carbonate or hydroxide with sterically hindered boronic acids [58].

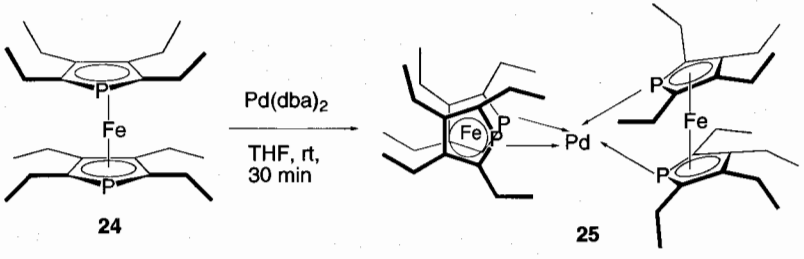
Most recently, Colobert et al. have reported that biaryl coupling between sterically hindered boronic acids and aryl iodides in the presence of a catalytic amount of $Pd(PPh_3)_4$ or $Pd(OAc)_2/PPh_3$ and CsF as a base in DME at 70 °C provides good to excellent yields in short reaction times. These coupling reactions were then applied to investigate the asymmetric Suzuki coupling synthesis of 2,2′-dimethoxy-1,1′-dinaphthalene using various chiral ligands (Equation 51) [64].



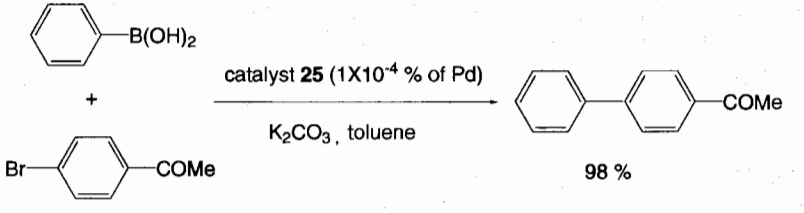
(51)

3.2.1.4 Modified Catalysts and Ligands

Octaethyldiphosphaferrocene (**24**) has been prepared (Equation 52) and the structure determined by X-ray analysis. Ligand **24** reacts with $[Pd(dba)_2]$ to yield the bis(octaethyldiphosphaferrocene)palladium(0) complex (**25**), which behaves as an efficient catalyst for the coupling reaction between phenylboronic acid and 4-bromoacetophenone in refluxing toluene. A conversion of 98% was obtained with 1×10^{-4}% of catalyst (TNO = 9.80×10^5) (Equations 52 and 53) [65].

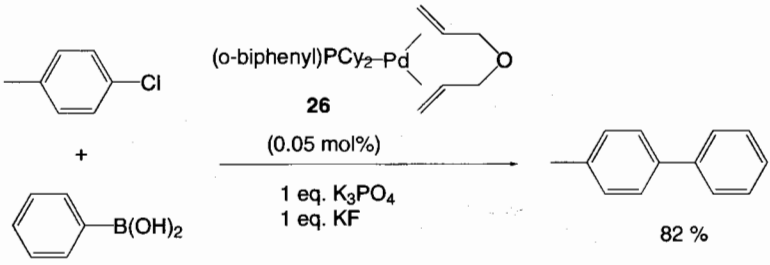


(52)



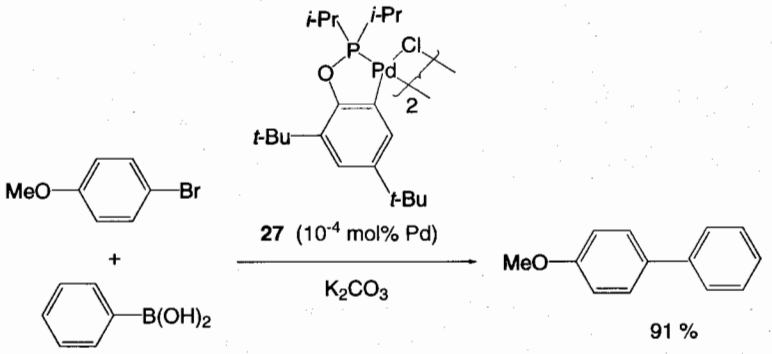
(53)

Various palladium(0) monophosphine complexes of 1,6-diene have been prepared from tmedaPd$(CH_3)_2$, PR_3, and the corresponding 1,6-dienes. These molecularly defined Pd complexes catalyzed the Suzuki coupling of aryl chlorides with phenylboronic acid more efficiently than traditional Pd(II)-PR_3 pre-catalysts. Best results were achieved with the 1,6-diene complex containing Buchwald's ligand (**26**). With only 0.05 mol% of the catalyst, good to excellent yields of biaryls were obtained from activated (2-chlorobenzonitrile, 97%), non-activated (4-chlorotoluene, 82%, chlorobenzene, 87%) and deactivated (4-chloroanisole, 72%) aryl chlorides (Equation 54) [66].



(54)

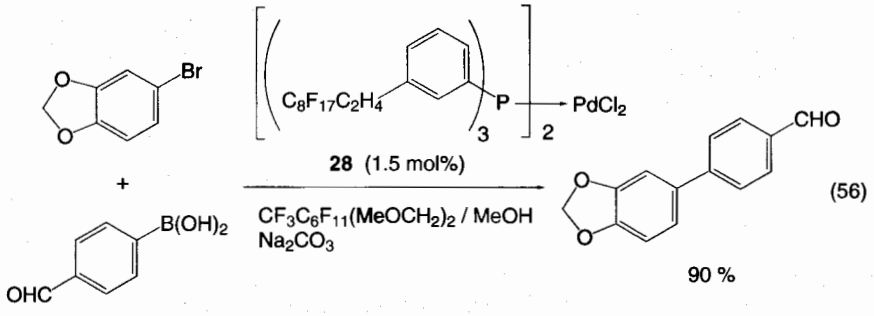
Several palladium(II) complexes containing mono-, bi- and tridentate carbene ligands were synthesized, characterized, and applied as catalysts in C–C coupling reactions. Such complexes proved to be highly stable and especially efficient catalysts for intermolecular Suzuki coupling reactions, giving turnover numbers of up to 177500 [67]. Phosphinite-based palladacycles show extremely high activity in the Suzuki coupling of both sterically hindered and electronically deactivated aryl bromides, especially in the presence of one equivalent of free ligand. For instance, Bedford and Welch synthesized such a complex, **27**, which was an effective catalyst for the coupling, as shown in Equation 55 [68].



(55)

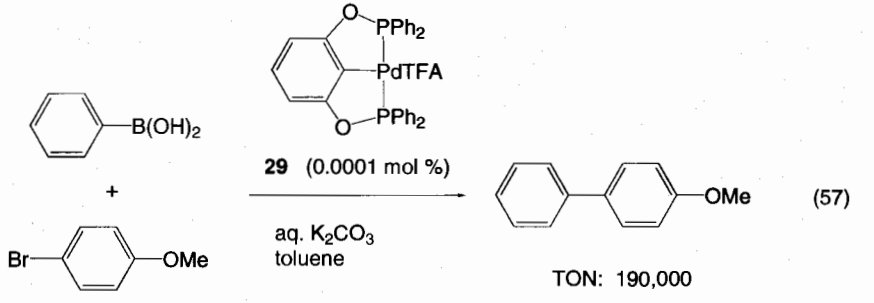
Imidazolium-linked *ortho*-cyclophane reacts with nickel(II) and palladium(II) salts in the presence of acetate base to afford complexes where a metal centre is bound by a pair of heterocyclic carbenes, which themselves are part of a cyclophane skeleton. These cyclophane-metal complexes have been characterized by NMR spectroscopy and X-ray diffraction studies. They are highly active as promoters of Suzuki couplings [69].

Suzuki aromatic–aromatic couplings were performed in high yields in a fluorous biphasic system by applying the four differently perfluoro-tagged Pd complexes **28**, which showed catalytic activity in the coupling of electron-rich or electron-deficient bromoarenes and arylboronic acids. Furthermore, such Pd complexes were recycled several times without a significant decrease in coupling yields (Equation 56) [70].



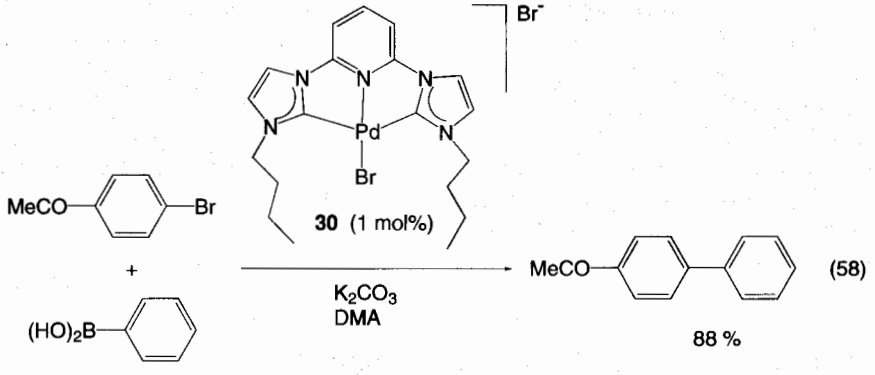
(56)

Fu et al. [71] and Buchwald et al. [72] independently reported phosphine derivatives as excellent ligands for the Suzuki reaction using palladium catalysts. However, the major drawback of these catalyst systems is that the phosphine ligands are comparatively difficult to prepare or are rather expensive. Bedford et al. observed that palladium complexes of inexpensive, easily synthesized bis(phosphinite) ligands such as **29** show high activity (Equation 57) [73].



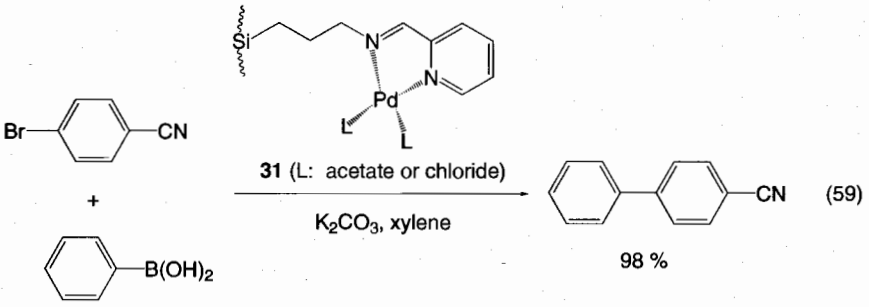
(57)

The synthesis and X-ray crystallographic characterization of a Pd complex **30** with a rigid C,N,C-tridentate pincer carbene ligand was investigated. Suzuki coupling reactions are catalyzed by **30**; the reaction is unaffected by air (Equation 58) [74].



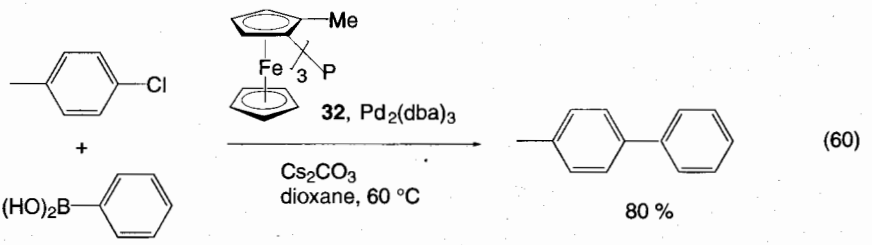
(58)

Some progress has been made in the use of solid-supported reagents for the Suzuki reaction, e.g. the combination of alumina-supported fluorides and palladium powder is effective in the coupling of arylboronic acids with iodobenzenes [75]. However, the reaction is much less effective with bromobenzenes and there is no evidence for the recyclability of the palladium, an essential aspect of the process on environmental and economic grounds. Most recently, Clark et al. have reported an entirely novel heterogeneous palladium (**31**) catalyst [76]. This novel heterogeneous palladium-catalyzed Suzuki reaction system is very effective with bromobenzenes, uses only hydrocarbon solvents, and requires very small amounts of solid palladium catalysts that are entirely recoverable and reusable. One additional salient feature of the catalyst is that it does not require addition of phosphines – thus improving the atom economy of the reaction. While reducing process costs, it also eliminates side reactions that may occur between arylphosphines and arylboronic acids. The overall outcome of these improvements may lead to more cost effective industrial processes and to the reduction of unwanted wastes (Equation 59) [76].



(59)

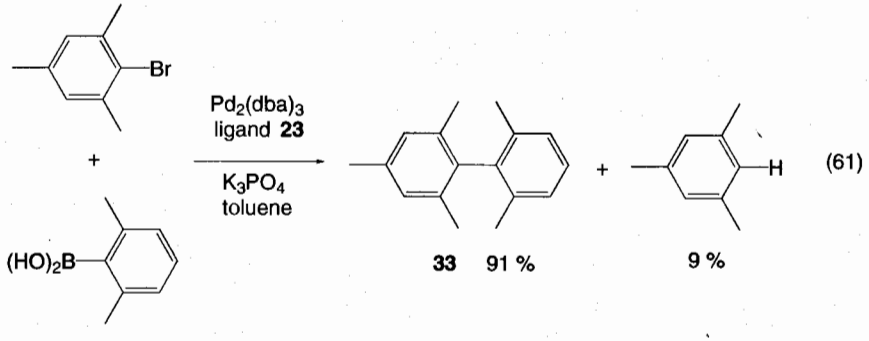
(pS,pS,pS)-Tris(2-methylferrocenyl)phosphine 32 was synthesized from (*S*)-ferrocenyl-4-(1-methylethyl)oxazoline. In combination with $Pd_2(dba)_3$ this novel C3-symmetric ligand generates a catalyst for the Suzuki reaction of aryl chloride substrates, and these reactions proceed readily at 60 °C in dioxane (Equation 60) [77]. .



(60)

Although the Suzuki coupling reaction is one of the most powerful C–C bond-forming transformations available in synthetic organic chemistry, limited success has been realized in reactions involving sterically hindered substrates. Thus, a general method for the coupling of two hindered arenes, where each reactant possesses two ortho substituents, has yet to be realized. Johnson and Foglesong reported a

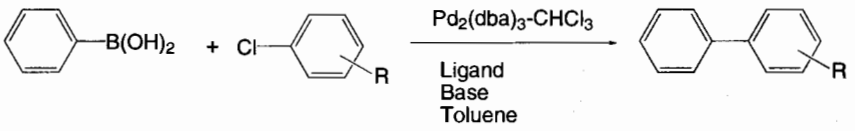
Suzuki coupling to prepare an unsymmetrical biaryl with tetra-ortho substitution in 12% yield [78]. Fu et al. reported an example of the preparation of a tetra-ortho substituted biaryl in 76% yield (Negishi coupling); however, the two ortho substituents were smaller than a methyl group [79]. In the initial study on Suzuki coupling with biphenyl-based ligands by Buchwald, significant amounts of aryl bromide reduction were observed [80]. Most recently, the Buchwald group has shown that phenanthrene-based ligand **23** gives superior results. The reaction proceeded to completion in less than 24 h with 4 mol% Pd and 8 mol% ligand **23**, affording the biaryl **33** in 91% with only 9% of mesitylene (Equation 61) [61]. To determine what feature made **23** superior in this challenging cross-coupling, they prepared and characterized the **23**/Pd complex, and confirmed that the key features of this structure are the shorter C9–Pd and C10–Pd bond distances (2.298 and 2.323 Å, respectively). Similar Pd–aryl interactions have been reported in Pd(II) complexes [81]. The C9–C10 bond of phenanthrene is likely to be a better π-donor than a phenyl or naphthyl moiety, as it resides in a less aromatically stabilized ring [82].



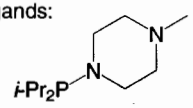
(61)

Novel electron rich, amine functionalized phosphines such as **34** and **35** have been reported and shown to belong to an unusual class of ligands that can activate palladium complexes to catalyze the Suzuki coupling reaction of chloroarenes. Table 3.2 shows some of these results. [83].

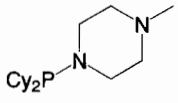
Table 3.2 Suzuki coupling of phenylboronic acid with a selection of aryl chlorides.



Ligands:



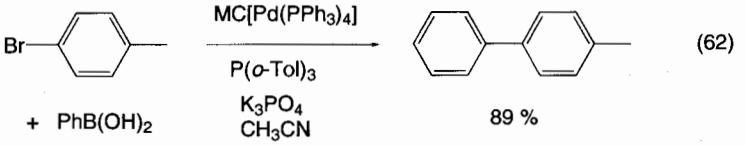
34



35

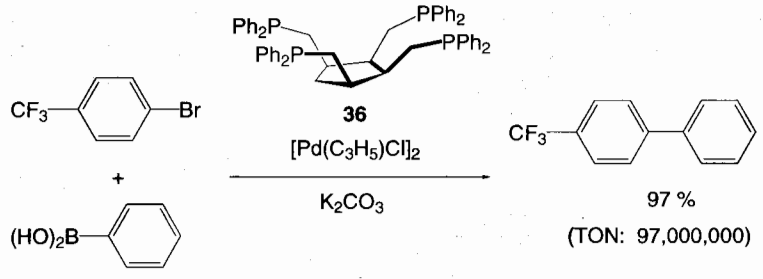
Ligand	Aryl chloride	Base	Conversion (%)
34	*p*-$CF_3C_6H_4$	K_3PO_4	100
34	*m*-$NO_2C_6H_4$	K_3PO_4	100
34	*p*-CNC_6H_4	K_3PO_4	100
35	*p*-MeC_6H_4	CsF	93
35	*p*-$MeCOC_6H_4$	CsF	100
35	*m*-$CHOC_6H_4$	CsF	100

Akiyama and Kobayashi reported the use of microencapsulated triphenylphosphine palladium catalysts for Suzuki coupling. The microencapsulated $Pd(PPh_3)_4$ [$MC(Pd(PPh_3)_4)$] was prepared by dissolving polystyrene in cyclohexane at 40 °C and adding $Pd(PPh_3)_4$. The resultant mixture was then stirred for 1 h at this temperature, slowly cooled to 0 °C, and hexane was added to harden the capsule walls. The mixture was then left to stand at room temperature for 12 h, after which the catalyst capsules were washed with acetonitrile and dried at room temperature. Suzuki coupling reactions of boronic acids with aryl bromides proceeded smoothly in the presence of $MC(Pd(PPh_3)_4)$ to afford the corresponding products in high yields (Equation 62) [84].



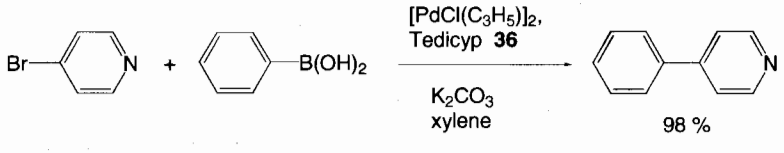
(62)

A new tetraphosphine, *cis-cis-cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (**36**, Tedicyp) has been synthesized and used in palladium-catalyzed reactions. This tetraphosphine in combination with $[Pd(C_3H_5)Cl]_2$ affords a very efficient catalyst for the Suzuki coupling reaction, with a turnover of 97 000 000 (Equation 63) [85].



(63)

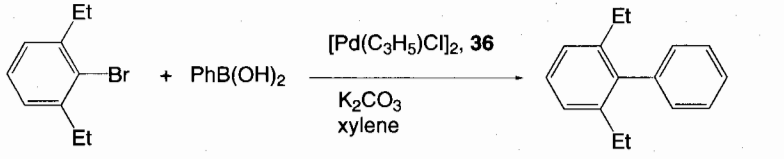
The Tedicyp (**36**)/$[PdCl(C_3H_5)]_2$ system catalyzes the Suzuki cross-coupling of heteroaryl bromides with arylboronic acids with a very high substrate/catalyst ratio in good yields. Substrates such as pyridines, quinolines, thiophenes, an indole, a pyrimidine or a furan have been used successfully (Equation 64) [86].



(64)

Ratio substrate/catalyst: 1 000 000

Furthermore, the Tedicyp/$[PdCl(C_3H_5)]_2$ system efficiently catalyzes the Suzuki coupling of sterically hindered substrates. Very high turnover numbers can be obtained for the coupling of sterically hindered aryl bromides with benzeneboronic acid or for the coupling of bromobenzene with sterically hindered arylboronic acids. Conversely, the formation of tri-ortho-substituted biaryl adducts requires a high catalyst loading (Equation 65) [87].

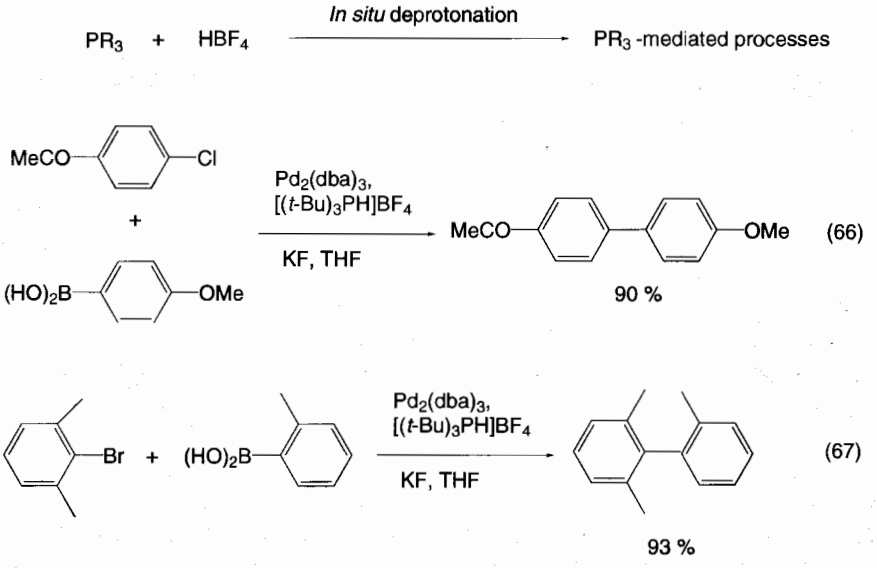


(65)

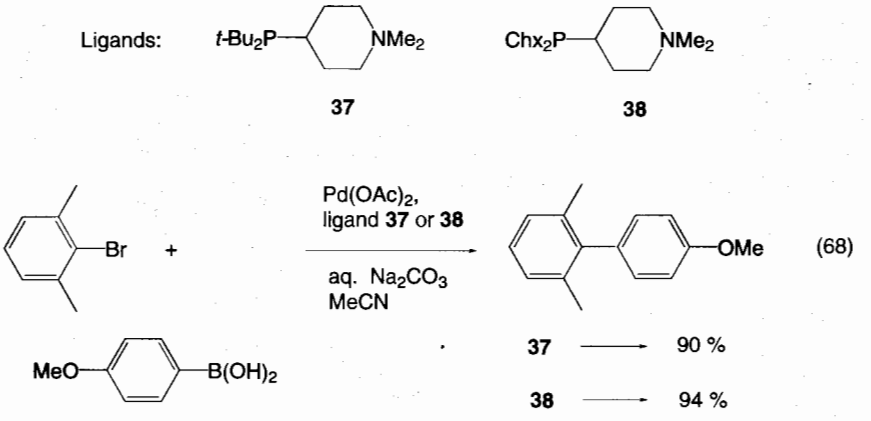
88 % (Turnover 1,000,000)

Until now, triarylphosphines (e.g., PPh_3), which are typically air-stable, have been the predominant focus of ligand study in transition metal catalysis. Trialkylphosphines, however, have been relatively neglected, probably largely because many are air-sensitive, which renders them more difficult to handle than triarylphosphines. Thus, even though trialkylphosphine ligands furnish unusual, sometimes unique, reactivity in a range of transformations, their utility is compromised by their sensitivity to oxidation. Most recently, Fu's group has examined a simple but powerful strategy for addressing this problem; convert air-sensitive trialkylphosphines into air-stable phosphonium salts via protonation on phosphorus. These robust salts serve as

direct replacements for the corresponding phosphines (simple deprotonation under the reaction conditions by a Brønsted base liberates the trialkylphosphine) in a diverse set of applications, including Suzuki coupling reactions (Equations 66 and 67) [88].

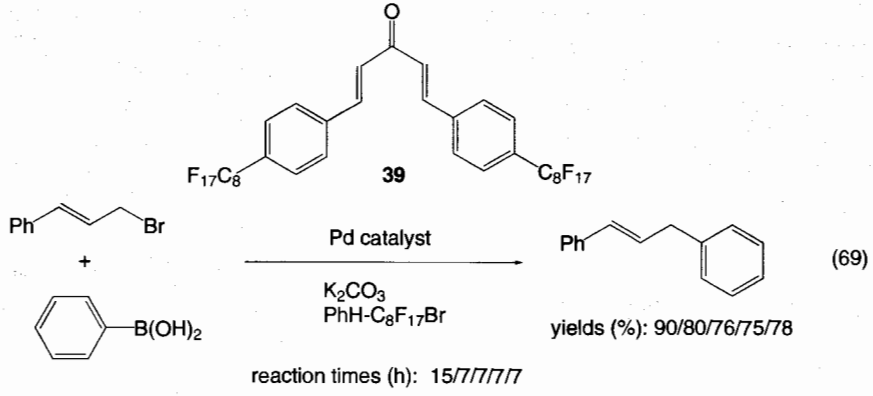


Aqueous-phase, palladium-catalyzed coupling reactions are of interest as environmentally benign synthetic methods that would decrease the use of volatile organic solvents and simplify catalyst recovery. Water-soluble phosphines, such as sodium tri(3-sulfanotophenyl)phosphine (TPPTS), have been applied to aqueous-phase Suzuki coupling reactions of aryl bromides [89], but the activity of these systems remains too low to be industrially viable. Water-soluble catalysts with increased activity toward aryl bromides and chlorides are necessary for wider applications of aqueous-phase catalyst systems. Recently, sterically demanding, water-soluble alkylphosphines **37** and **38** have been found to give highly active catalysts for Suzuki coupling of aryl bromides in aqueous solvents. Various aryl bromides and boronic acids were coupled in excellent yields (Equation 68) [90].



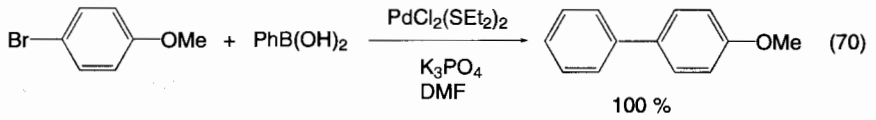
(68)

Water-soluble calix[*n*]arenes are powerful receptors for non-polar substrates in aqueous solution. These compounds are promising candidates as carrier molecules for the transport of non-polar substrates through bulk water as well as inverse phase-transfer catalysts, as proven for the Suzuki coupling of iodobenzene with phenyl boronic acid [91]. 1,5-bis(4,4′-bis(perfluorooctyl)penta-1,4-dien-3-one (**39**) stabilizes palladium(0) nanoparticles (transmission electron microscopy) formed in the reduction of palladium dichloride with methanol. These palladium colloids are soluble in perfluorinated solvents, and they are efficient recoverable catalysts for Suzuki cross-coupling under fluorous biphasic conditions (Equation 69) [92].



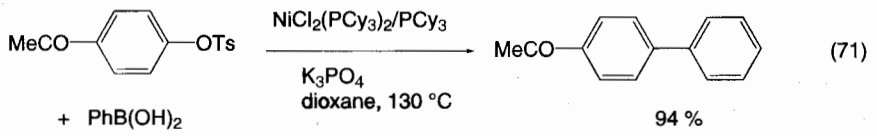
(69)

$PdCl_2(SEt_2)_2$ promotes efficiently the Suzuki coupling reaction of aryl bromides and chlorides with arylboronic acids under mild conditions. This method tolerates various functional groups (Equation 70) [93].



(70)

$NiCl_2(PCy_3)_2$ associated with PCy_3 promotes the selective cross-coupling of aryltosylates with arylboronic acids under relatively mild reaction conditions, and various functional groups are tolerated in both arene reactants. This is one of the simplest, most efficient experimental procedures for coupling arylboronic acids with aryl tosylates reported to date (Equation 71) [94].



(71)

The catalytically active species are probably $Ni(PCy_3)_n$ formed from the sequence involving arylboronic acid transmetallation and reductive elimination (Figure 3.1). Indeed, in all cases 2–3% of the arylboronic acid homocoupled product was observed. The general mechanism of a transition metal catalyzed cross-coupling reaction between organic electrophiles and organometallic reagents involving sequential oxidative addition, transmetallation, and reductive elimination can explain the observed results. In the first step, the electron-rich Ni(0) complex formed is stabilized by PCy_3, and it then undergoes the oxidative addition to aryl tosylates [94].

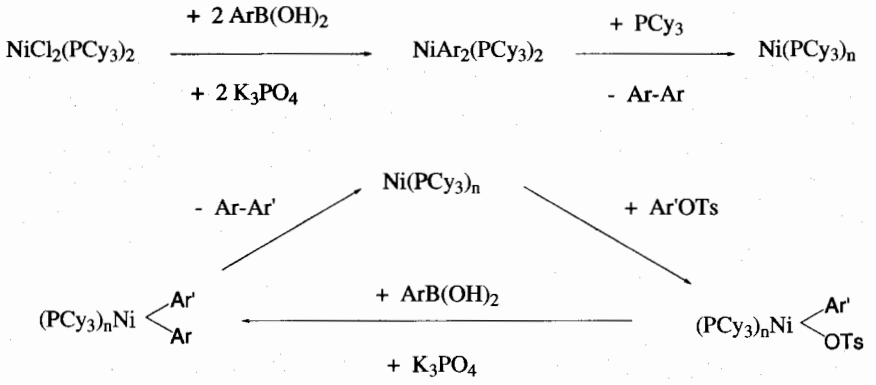
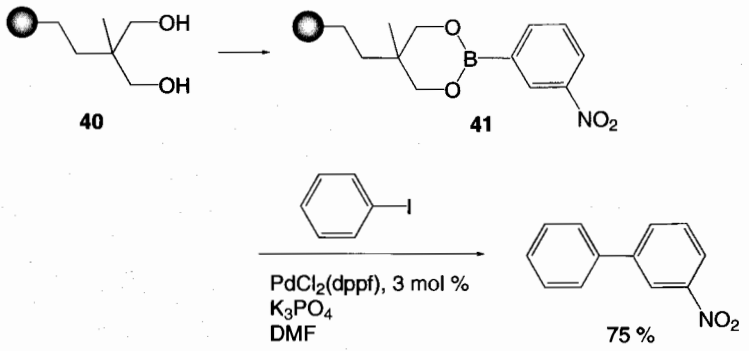


Figure 3.1 Reaction path for the Ni-catalyzed Śuzuki cross-coupling reaction of aryltosylates.

3.2.1.5 Solid-phase Synthesis (Combinatorial Methodology)

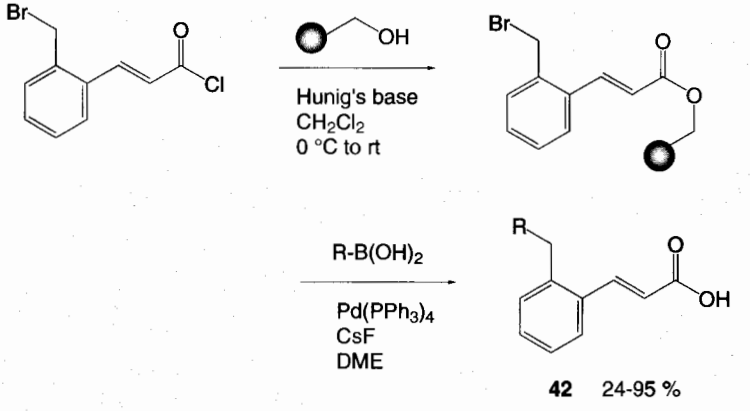
Solid-phase reactions play an important role in parallel synthesis and combinatorial chemistry, particularly in the area of medicinal chemistry, where their potential has emerged as a result of the possibility of automation. Considerable attention has been focused on adapting and exploiting the advantages of solid-phase synthesis (SPS) to produce libraries of such organic compounds. In this context, transition metal-pro-

moted reactions serve as efficient methods because they proceed under mild conditions and are compatible with many functional groups. For instance, the solid-phase Suzuki coupling has been largely developed mainly by the reaction of a resin-bound aryl halide with a solution-phase boronic acid [95]. Recently, the viability of solid-supported boronic acids as reagents for Suzuki couplings was demonstrated successfully. Namely, Carboni et al. reported the preparation of a macroporous support (**40**) that can be employed to efficiently immobilize and transform functionalized arylboronic acids [96]. One of the major advantages of this boronate linker system is its possible use in a resin capture process [97]. The same authors reported the successful use of supported boronic acid **41** in the Suzuki coupling (Equation 72) [98].



(72)

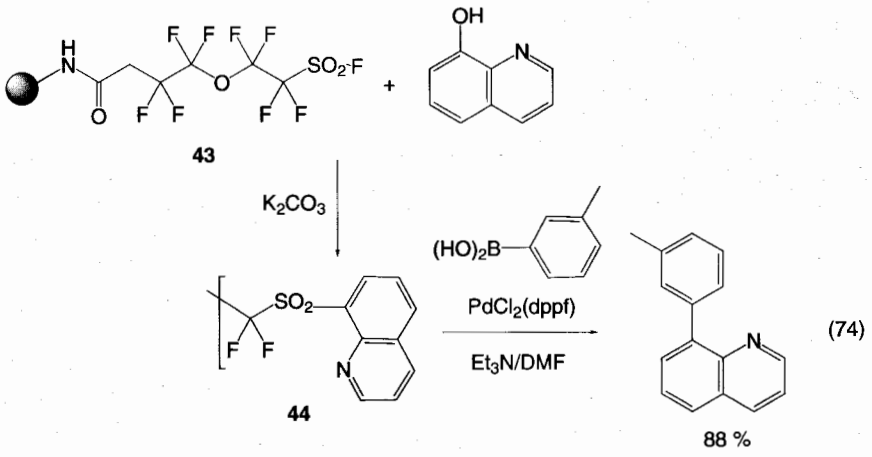
Human EP3 prostanoid receptors can be obtained by Suzuki coupling reaction of a solid-supported benzyl bromide using various boronic acids (Equation 73) [99]. Yields obtained for the reaction were in the range of 24–95% of isolated arylmethyl cinnamic acid **42** after cleavage from the Wang resin.



(73)

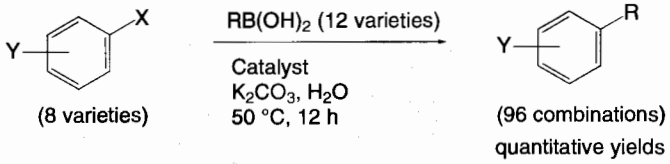
Different polystyrene–divinyl benzene cross-linked resins were prepared, and the influence of resin cross-linking on the solid-phase chemistry of a Suzuki coupling has been reported [100]. Todd and Abell described a novel chemical tagging strategy

for combinatorial solid-phase chemistry. The tags used are para-substituted alkyl phenols, with the first tags attached directly to the chloromethyl polystyrene and subsequent tags attached via Suzuki couplings using either aryl diboronic acids or aryl iodides. The identities of the tags attached to a single bead are determined by the high-resolution accurate mass technique of Fourier transform ion cyclotron resonance mass spectrometry [101]. Pan et al. reported the preparation of a perfluoroalkylsulfonyl fluoride resin **43** [102] and its application in Suzuki coupling reactions to prepare **44** (Equation 74) [103].

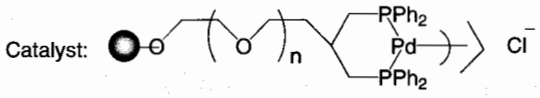


(74)

Suzuki couplings of aryl halides (eight varieties) and aryl- or vinylboronic acids (12 varieties) have been reported in water in the presence of a palladium complex of an amphiphilic polystyrene–poly(ethylene glycol) copolymer resin-supported *N*-anchored 2-aza-1,3-bis(diphenylphosphino)propane ligand and potassium carbonate to give uniform and quantitative yields of the corresponding biaryls products (96 combinations) (Equation 75) [104].

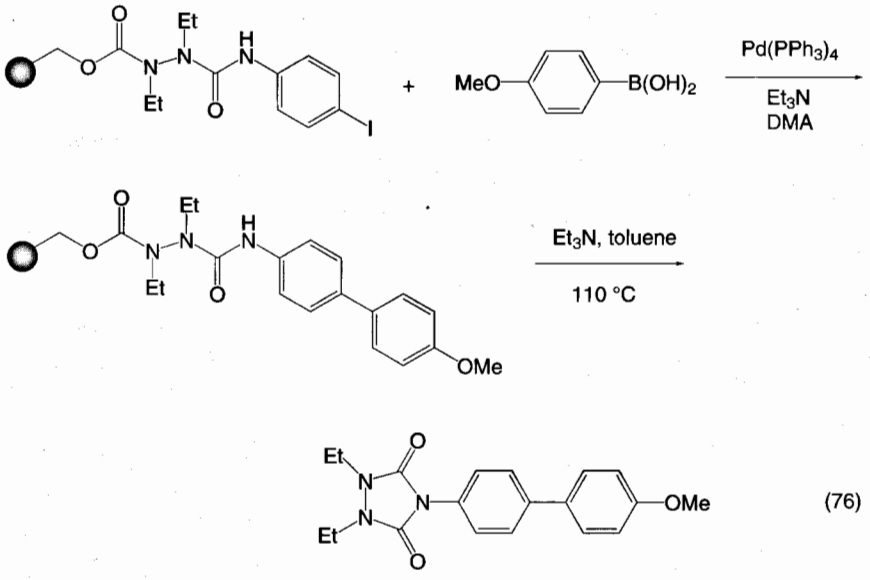


(75)



Solid-phase syntheses of 1,2,4-trisubstituted urazole and thiourazole derivatives have been accomplished. Suzuki coupling of the immobilized reactant gives the expected coupling product. Subsequent heating of the resin in the presence of triethy-

lamine or potassium *t*-butoxide induced cyclization and released the desired (thio)-urazole into solution. Structural diversity can be further expanded by performing the palladium-mediated Suzuki coupling reaction (Equation 76) [105].



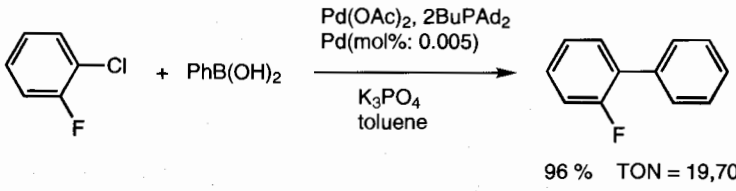
(76)

25 % based on the loading of Wang resin

The usefulness of the diethanolamine polystyrene resin (DEAMPS) developed by Hall and co-workers [106] has been demonstrated in an example of resin-to-resin Suzuki coupling [107].

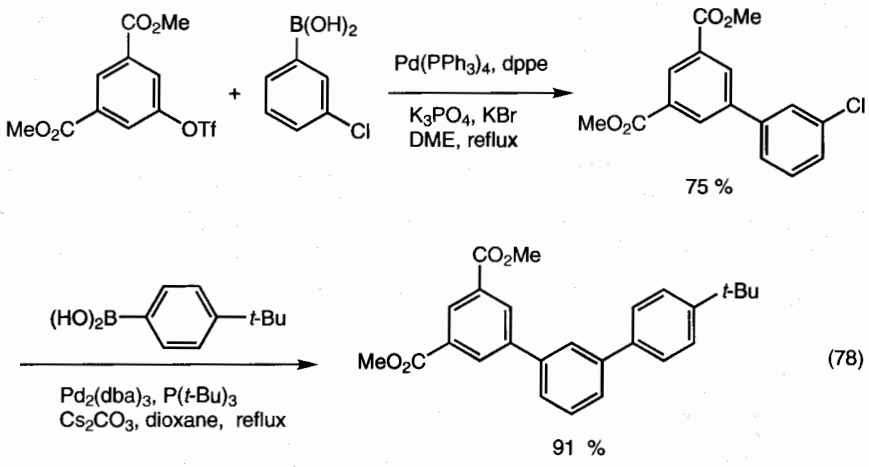
3.2.2
With Other Organic Halides, including Aryl Chlorides and Electrophiles

In aromatic–aromatic cross-coupling reactions, cheap, readily accessible aryl chlorides are particularly important as starting materials from an industrial viewpoint. Recently, several research groups, especially Fu's [71] and Buchwald's [72, 108] have reported very efficient methods for the coupling of aryl chlorides. Aside from recent methods, despite the good yields in many Suzuki reactions of chloroarenes, comparatively large amounts of catalyst are generally required (1–3 mol%) [109]. Beller et al. reported a new catalyst system, with which they achieved the coupling of nonactivated and deactivated aryl chlorides highly efficiently in good yields with generally only 0.005 mol% palladium and, thus, under industrially viable conditions [110]. For instance, as a new and efficient catalyst system, they used diadamantyl-*n*-butylphosphane ($BuPAd_2$) as a ligand and found that it to be extremely reactive. Equation 77 shows a typical example.



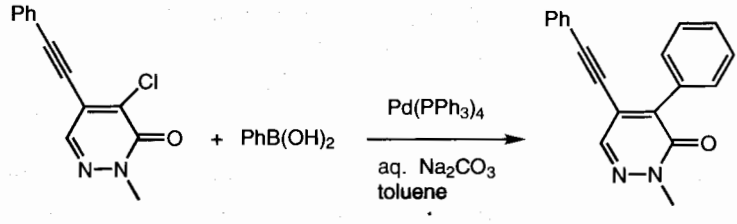
96 % TON = 19,700 (77)

A series of potentially selective inhibitors of dihydroorotate dehydrogenase (DHODH) were synthesized via interactive, chemoselective Suzuki cross-couplings utilizing biaryl chlorides as key intermediates (Equation 78) [111].

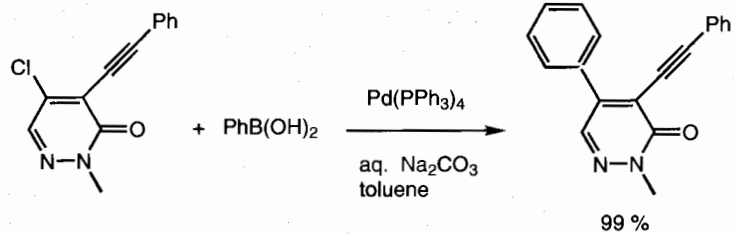


(78)

Suzuki coupling reactions where also achieved on substrates that lead to 4-aryl-5-phenylethynyl- and 5-aryl-4-phenylethynyl-2-methyl-3(2*H*)-pyridazinones, in excellent yields (Equations 79 and 80, respectively) [112].

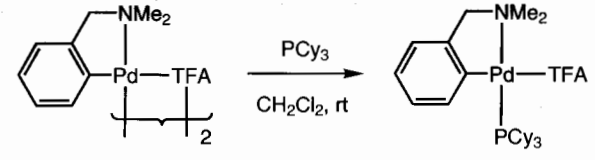


86 % (79)

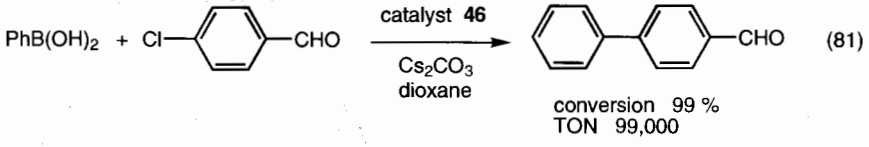


99 % (80)

Recently, Bedford and Cazin reported the use of orthometallated complex **45** as a catalyst precursor as it is readily accessible from *N,N*-dimethylbenzylamine, which is commercially available and inexpensive. Complex **45** reacts readily with tricyclohexylphosphine in dichloromethane to generate adduct **46**, which shows good air- and moisture-stability, and is a highly active catalyst for Suzuki coupling of aryl chlorides (Equation 81) [113].

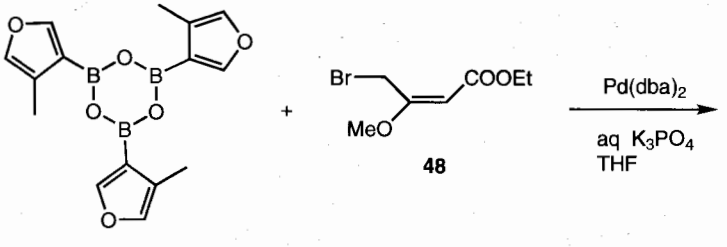


45 **46**

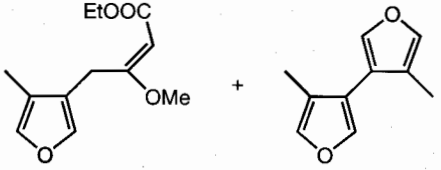


(81)

Suzuki coupling of boroxine **47** with ethyl 4-bromo-3-methoxycrotonate (**48**) provides the desired product **49** in 60% yield, together with **50** (20%) (Equation 82) [114].



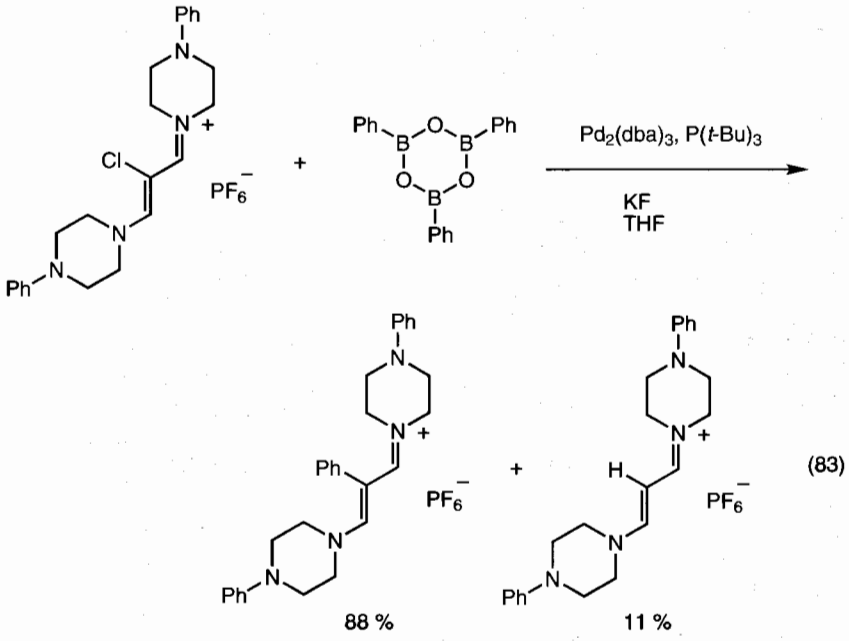
47 **48**



49 60 % **50** 20 %

(82)

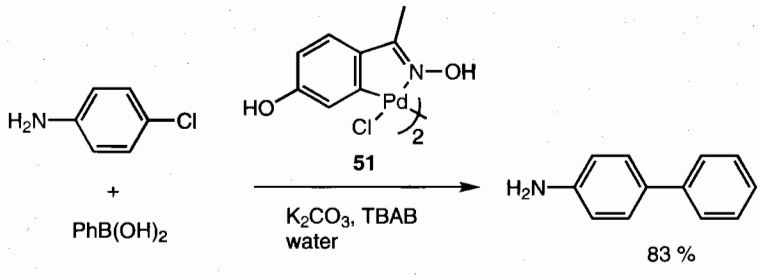
Recently, Davies et al. have observed that boronic acids, esters and boronic anhydrides are partners in Suzuki coupling reactions with various β-chlorovinylamidinium salts to give the desired β-arylvinylamidinium salts. Among boron partners, boronic anhydrides give better yields (up to 88%). Reduction is a competing reaction pathway (Equation 83) [115].



(83)

The importance of biaryl units as components of many kinds of compounds, pharmaceuticals, herbicides, and natural products, as well as engineering materials has attracted enormous interest from the chemical community. Palladium-catalyzed Suzuki coupling is the most important and efficient strategy for the construction of symmetrical and unsymmetrical biaryl compounds, as described previously. Industrially, some important goals need to be realized for the development of this process: the functionalization of inexpensive and readily accessible aryl chlorides and the use of water as a safe, inexpensive solvent. Furthermore, to avoid the use of inert atmospheric conditions, air-stable, efficient, and nontoxic catalysts are desired. Both electron-deficient and electron-rich aryl chlorides have been activated by palladium complexes in the presence of expensive and toxic phosphane [42, 71, 110, 116], phosphites [117], phosphane oxides [118], palladium N-heterocyclic carbene complexes [119], and palladium on carbon [120]. However, palladacycles have only been used as catalyst with electron-deficient aryl chlorides [121]. Suzuki coupling reactions with organoboranes are generally carried out in a mixture of an organic solvent and an aqueous inorganic base. Few reactions were reported in neat water [122].

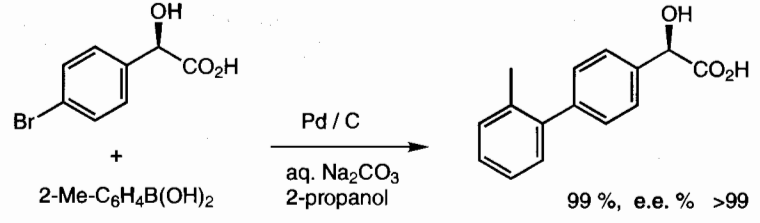
Most recently, Botella and Najera have reported that oxime-derived palladacycles such as **51** are air- and water-stable catalysts that are suitable for cross-coupling reactions of different aryl and heteroaryl chlorides with boronic acids in neat water (Equation 84) [123].



(84)

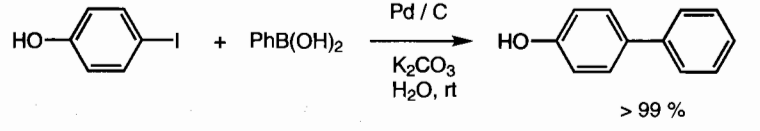
3.2.3 Miscellaneous

A library of enantiomerically pure mandelic acid derivatives has been prepared in excellent yields using a palladium-on-carbon catalyzed Suzuki reaction. During the coupling reaction, no racemization was observed (Equation 85) [124].



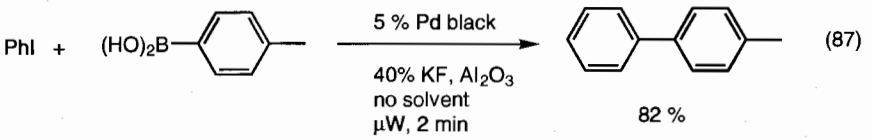
(85)

Pd/C was found to catalyze the Suzuki coupling reaction of halophenols in aqueous media. When halophenols were treated with areneboronic acids and a catalytic amount of 10% Pd/C (0.3 mol% Pd) in aqueous K_2CO_3 solution, the corresponding hydroxybiaryls were obtained in near quantitative yield. The palladium catalyst was easily recovered and reused (Equation 86) [125].



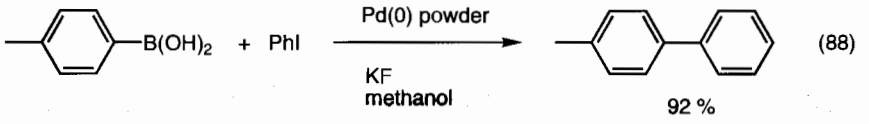
(86)

The development of a solventless, microwave-assisted Suzuki reaction utilizing a readily recyclable solid catalyst offers numerous benefits. These include the straightforward recovery of both product and catalyst, conservation of energy through the use of microwave irradiation, simple commercial scale up, and low waste protocols due to the absence of solvents. Recently, Kabalka et al. reported such a procedure for the reaction between aryl iodides and arylboronic acids or vinyl boronic acids in the presence of KF–Al_2O_3 as a base [75a] to provide excellent yields of expected coupled products (Equation 87) [75b].



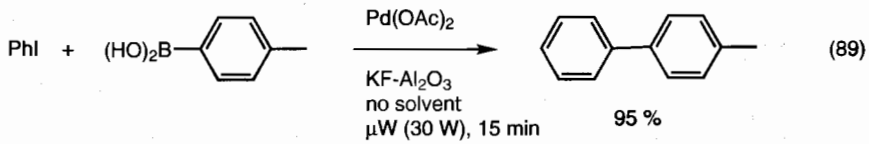
(87)

A ligandless Suzuki coupling reaction was described between arylboronic acids and aryl iodides in the presence of palladium powder and potassium fluoride to provide coupled products in excellent yields. Importantly, the palladium metal can be recovered and recycled by a simple decantation of the reaction solution. In one series of experiments, Kabalka et al. carried out eight consecutive preparations of 4-methylbiphenyl with no significant loss in product yields. In each case, the palladium powder was recovered by decantation, washed with methanol, and the experiment repeated (Equation 88) [126].



(88)

Hallberg et al. have shown that microwaves accelerate palladium-catalyzed reactions (e.g. Suzuki, Heck, Tsuji–Trost, Stille) in solution or with supported polymers [127]. Most recently, Villemin and Caillot have reported that, in the Suzuki reaction, the use of a ligand-free palladium catalyst, palladium acetate, without the use of solvent under microwave irradiation produces good yields of biphenyl products, one of which is shown in Equation 89 [128].

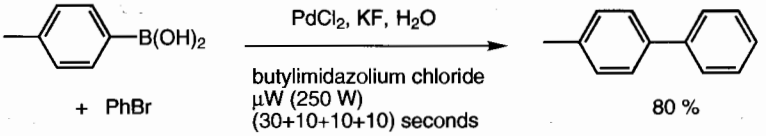


(89)

A series of poly(*N*-vinyl-2-pyrrolidone)-stabilized Pd nanoparticles with varying particle size were prepared by using the stepwise growth reaction. The effect of Pd particle size on the Suzuki reaction between phenylboronic acid and iodobenzene was investigated by the use of four Pd catalysts with mean particle sizes of 3.0, 3.9, 5.2, and 6.6 nm. The catalytic activity of the Pd nanoparticles was in the order of Pd (3.9 nm) > Pd (3.0 nm) ≈ Pd (5.2 nm) > Pd (6.6 nm), indicating that surface Pd atoms do not all have the same reactivity in this reaction. The general trend of increased catalytic activity with decreasing the particle size suggests that the low-coordination number vertex and edge atoms on the particle surface are active sites for the Suzuki reaction. The lower catalytic activity for the smallest Pd nanoparticles (3.0 nm) might be due to stronger adsorption of the reaction intermediates on the particle surface,

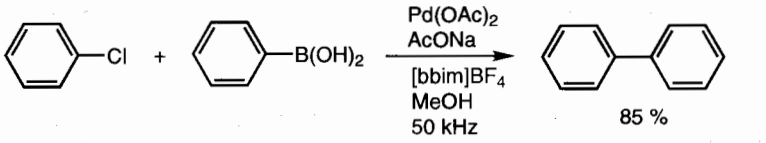
with the strongly absorbed species losing mobility and thereby decreasing the reaction rate [129].

The use of fused organic salts, consisting of ions, is emerging as a possible alternative in green chemistry. A proper choice of cations and anions is required to achieve ionic salts that are liquids at room temperature, and are appropriately termed room-temperature ionic liquids (RTILs). Common RTILs consist of *N,N'*-dialkylimidazolium, alkylammonium, alkylphosphonium or *N*-alkylimidazolium as cations [130]. Most of these ionic salts are good solvents for a wide range of organic and ionic materials and are stable enough to air, moisture, and heat. Ionic liquids are polar (but consist of poorly coordinating ions), are immiscible with a number of organic solvents, and provide polar alternatives for biphasic systems. An efficient solventless protocol for the preparation of a wide variety of ionic liquids has been reported by Varma et al., which requires a simple exposure of admixed 1-methylimidazole and alkyl halides to microwave irradiation in open glass containers. Under such ionic liquid conditions, Suzuki couplings have been carried out to provide good results, as shown in the example below (Equation 90) [131].



(90)

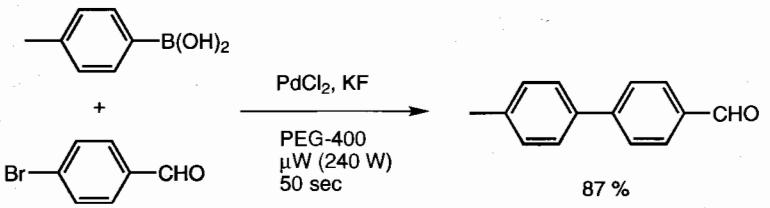
Suzuki reactions have also been conducted in conditions such as the use of 1,3-di-*n*-butylimidazolium tetrafluoroborate [bbim]BF_4 at 110 °C in the presence of phosphine ligands with several advantages [132]. In this investigation, however, chlorobenzene was practically non-reactive, affording only traces of biaryl product. Most recently Srinivasan et al. have observed that palladium-catalyzed Suzuki couplings of halobenzenes, including chlorobenzenes, with phenylboronic acid are achieved at ambient temperature (30 °C) in the absence of a phosphine ligand using the ionic liquid [bbim]BF_4 with methanol as co-solvent under ultrasonic irradiation, providing coupled products in excellent yields (Equation 91) [133].



(91)

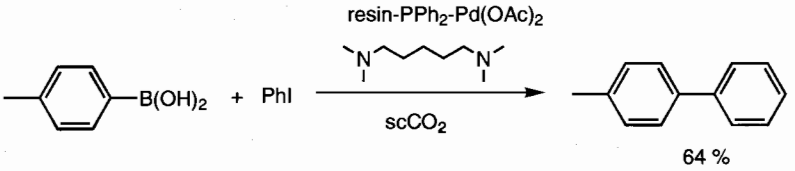
Dupont et al. have reviewed ionic liquid (molten salt) phase organometallic catalysis, including the Suzuki coupling reaction [134].

Polyethylene glycol (PEG) is an inexpensive, non-toxic reaction medium for the microwave-assisted Suzuki cross-coupling of arylboronic acids with aryl halides. This environmentally friendly microwave protocol offers ease of operation and enables recyclability of catalyst in the synthesis of various substituted biaryls, employing palladium chloride as catalyst and potassium fluoride as the base (Equation 92) [135].



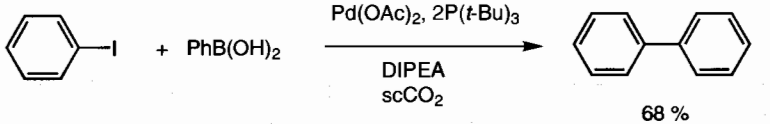
(92)

Supercritical carbon dioxide ($scCO_2$) has attracted much recent interest as an environmentally benign alternative to many toxic organic solvents. It is non-toxic, inexpensive, universally available and affords facile separation from products by simple depressurization. Commercially available polystyrene-supported amine and phosphine resins facilitate palladium-mediated Suzuki reactions in $scCO_2$. For example, treatment of tolyl boronic acid with iodobenzene and the base *N,N,N,N*-tetramethylhexanediamine in the presence of the polymer-supported phosphine-Pd catalyst afforded the biaryl product, which was isolated simply by venting the liquid CO_2 into a beaker containing EtOAc. Washing the remaining resin and amine salt with liquid CO_2 afforded the desired product in 64% yield (Equation 93) [136].

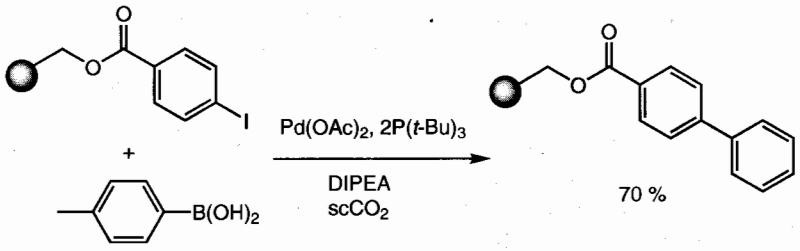


(93)

However, the practical use of supercritical carbon dioxide has been limited by its solvating power. Although $scCO_2$ dissolves most non-polar compounds of low molecular mass, many catalysts, substrates and reagents are only poorly soluble. Most recently, it was reported that Suzuki reactions proceed in good yield in $scCO_2$ in the presence of palladium acetate and tri-*tert*-butylphosphine, with DIPEA (*N,N*-diisopropylethylamine) as the base (Equations 94 and 95) [137].



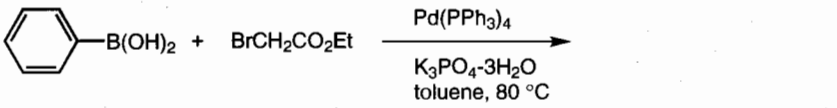
(94)



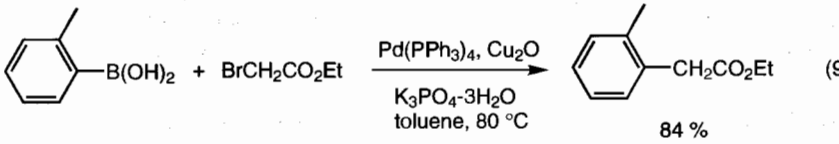
(95)

Poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) triblock copolymers were first applied successfully as a phase transfer reagent in two-phase Suzuki carbon–carbon coupling reactions. The use of such polymeric reagents in micellar and phase-transfer systems has the advantage that they can be separated easily from the reaction mixture by means of a membrane [138].

Few studies have explored the coupling of haloacetate with organoboron compounds to expand the scope of Suzuki coupling reaction and develop a convenient and practical method for introducing the methylenecarboxy group into molecules [139]. Most recently, a remarkable co-catalysis by copper(I) oxide in the palladium catalyzed cross-coupling of arylboronic acids with ethyl bromoacetate was reported to afford **52**. According to Deng et al., under some conditions, using $Pd(PPh_3)_4$ as catalyst, the rate of the desired coupling reaction is lower than the redox, homo-coupling reactions of phenylboronic acid and the reductive reaction of ethyl bromoacetate, which lead respectively to biphenyl **53**, benzene **54**, and ethyl acetate **55**. However, the use of Cu_2O as a co-catalyst dramatically improved the coupling to give excellent yields of expected products (Equations 96 and 97) [140].



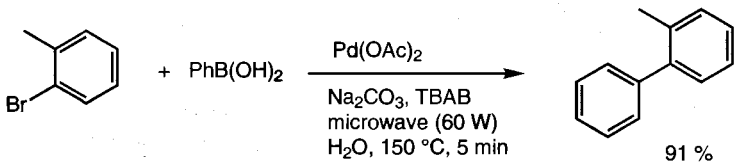
(96)



(97)

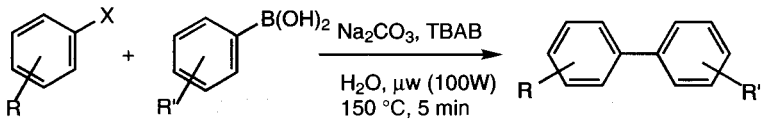
Leadbeater has reported the ligand-free palladium-catalyzed Suzuki reaction in water using microwave heating, which uses a low palladium loading (0.4 mol%), is fast (5–10 min reaction time), and is useful for couplings involving boronic acids and aryl iodides, bromides, and chlorides (Equation 98) [141]. Immediately thereafter, Leadbeater and Marco reported the scope and limitation of the transition-metal-free Suzuki-type coupling of aryl halides and arylboronic acids to form biaryls. The main findings are that the reaction works well for aryl bromides, water is necessary as a solvent for the reaction, and the optimum reaction temperature is 150 °C. The reaction is best performed using microwave promotion, with the exception of an electron-poor aryl bromide example where conventional heating may be used. Only a limited set boronic acids can be used as coupling partners; sodium carbonate is the best base for the reaction, and tetrabutylammonium bromide proves to be the best phase-transfer catalyst for the reaction. The reaction is limited to couplings between aryl halides and

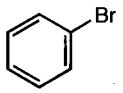
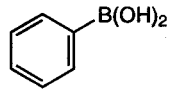
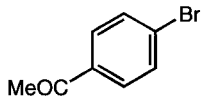
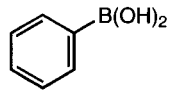
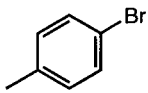
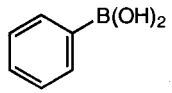
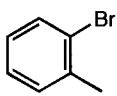
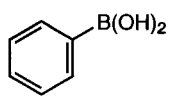
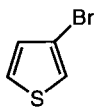
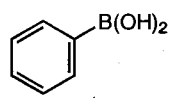
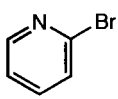
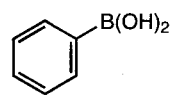
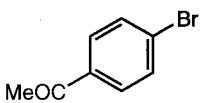
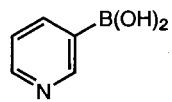
arylboronic acids, with sp^2–sp^3 couplings proving ineffective, and $NaBPh_4$ can be used in the place of phenylboronic acid as a phenylating agent. Some examples of these reactions are shown in Table 3.3 [142].



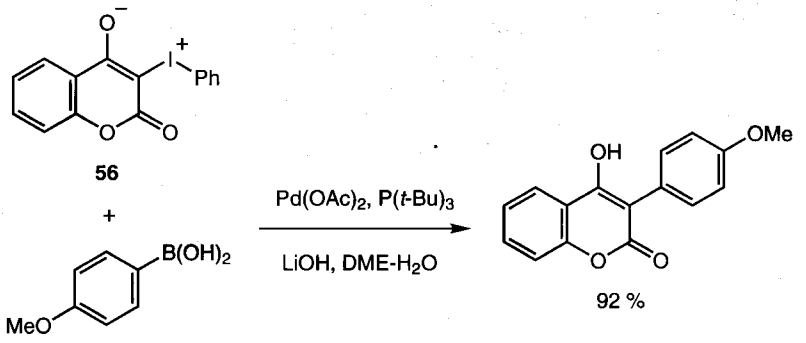
(98)

Table 3.3 Transition-metal-free Suzuki-type coupling of aryl halides and boronic acids in water using microwave heating.



Aryl halide	Boronic acid	Yield (%)
		90
		98
		82
		61
		0
		76
		0

A palladium-catalyzed Suzuki coupling reaction of phenyliodonium zwitterions **56** with aryl boronic acids has been developed. The unique characteristics of the mild reaction conditions and convenient synthetic accessibility of phenyliodonium zwitterions make this method a valuable tool for generating diversified 3-aryl-4-hydroxycoumarins (Equation 99) [143].



(99)

3.3 Conclusion

Carbon–carbon bond formation reactions employing organoboron compounds and organic electrophiles have been recognized recently as powerful tools for the construction of new organic compounds. Among such reactions, aromatic–aromatic (or heteroaromatic) couplings between aromatic boronic acids or esters and aromatic electrophiles, providing symmetrical and unsymmetrical biaryls selectively in high yields, have been used most frequently. The coupling reaction offers several advantages:

1. Easy availability of reactants
2. Mild reaction conditions
3. Water stability
4. Easy use of the reaction under both aqueous and heterogeneous conditions
5. Tolerance of a broad range of functional groups
6. High regio- and stereoselectivity in the reaction
7. Insignificant effect toward steric hindrance
8. Use of very small amounts of catalysts
9. Utilization as one-pot synthesis
10. Non-toxic, clean reaction

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4
Rhodium-catalyzed Additions of Boronic Acids to Alkenes and Carbonyl Compounds

Kazuhiro Yoshida and Tamio Hayashi

4.1
Introduction

Nucleophilic addition of organometallic reagents to electron-deficient compounds is fundamentally important in organic synthesis. In this field, organomagnesium and organolithium derivatives are most frequently used because of their high reactivity and ready availability. However, these organometallic reagents can tolerate only a few electrophilic groups. As a result, protection of functional groups is often required. An attractive strategy would be to activate milder nucleophiles that do not suffer from this problem of functional group tolerance.

The combination of rhodium catalysts and organoboronic acids has emerged recently as a powerful and ideal catalytic system in carbon–carbon bond forming reactions. This tremendous system overcomes the functional group protection issue, but can also apply to catalytic asymmetric synthesis, which can provide much chiral product using a small amount of a chiral catalyst. This chapter reviews the development and scope of the rhodium-catalyzed addition of boronic acids to organic electrophiles [1].

4.2
Addition of Organoboronic Acids to α,β-Unsaturated Ketones

In 1997 Miyaura published an important paper in which the conjugate addition of aryl- and alkenyl-boronic acids to α,β-unsaturated ketones was shown to proceed under catalysis by a rhodium complex [2]. In this work, a catalyst generated from $Rh(acac)(CO)_2$ and 1,4-bis(diphenylphosphino)butane (dppb) was used in aqueous solvents (Scheme 4.1). Conjugate addition takes place not only for β-unsubstituted enones such as methyl vinyl ketone but also for β-substituted enones such as 2-cyclohexenone, albeit in low yields. Notably, even enals undergo the chemoselective conjugate addition in high yields, indicating the great potential of this reaction.

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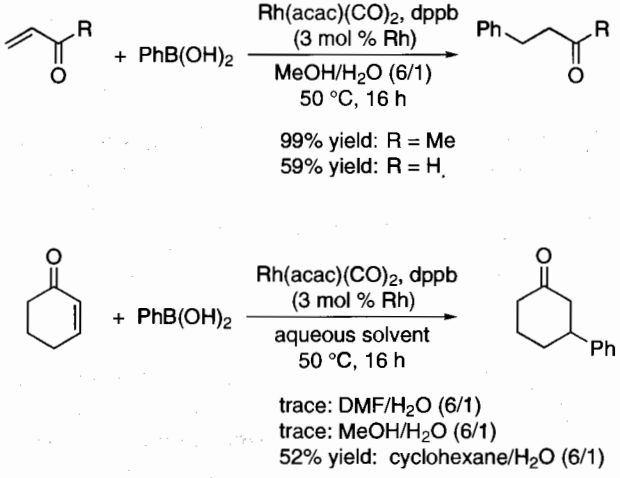
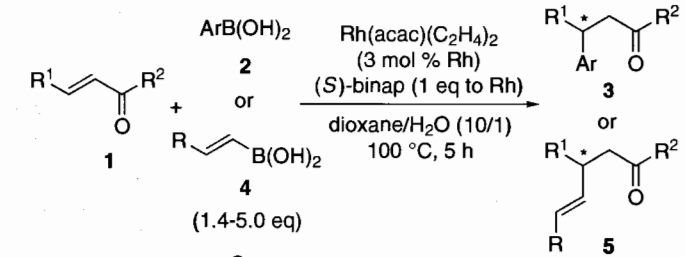
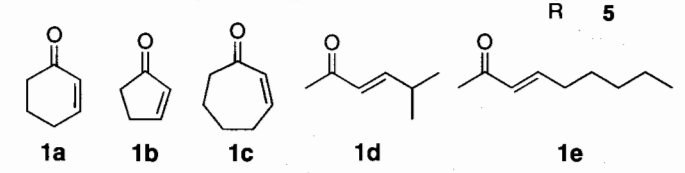
Organoboronic acids are not reactive toward enones in the absence of a rhodium catalyst, and their stability to oxygen and moisture allows one to handle them without special precautions. In this rhodium-catalyzed reaction, the use of aqueous solvent is essential and its role will be discussed in Section 4.3.

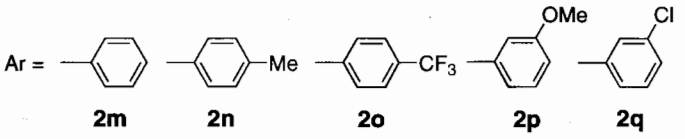


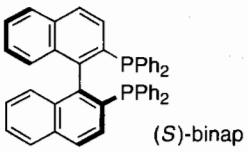
Scheme 4.1 Rhodium-catalyzed conjugate addition of phenylboronic acid to α,β-unsaturated ketones.

In 1998 Hayashi and Miyaura reported the first example of rhodium-catalyzed asymmetric conjugate addition [3]. After optimization of the reaction conditions, high enantioselectivities were achieved by use of (*S*)-binap as a chiral bisphosphine ligand (Scheme 4.2). On this occasion, the rhodium precursor was changed from $Rh(acac)(CO)_2$ to $Rh(acac)(C_2H_4)_2$, the temperature was increased to 100 °C, the solvent was changed to a 10:1 mixture of dioxane–water, and the reaction time was shortened to 5 h. The scope of the reaction is very broad. Under the conditions, the addition of phenylboronic acid (**2m**) to 2-cyclohexenone (**1a**) gave 99% yield of (*S*)-3-phenylcyclohexanone (**3am**) with 97% ee (Scheme 4.2, entry 1). Aryl groups substituted with either electron-donating or -withdrawing groups, 4-MeC_6H_4, 4-$CF_3C_6H_4$, 3-$MeOC_6H_4$, and 3-ClC_6H_4, were introduced onto 2-cyclohexenone (**1a**) with similar enantioselectivity by reaction with the corresponding boronic acids **2n–q** (entries 2–5). Asymmetric addition of 1-alkenylboronic acids was as successful as that of arylboronic acids, with (*E*)-1-heptenylboronic acid (**4m**) and (*E*)-3,3-dimethyl-1-butenylboronic acid (**4n**) giving the corresponding alkenylation products **5am** and **5an** of over 90% ee (entries 10–12). Cyclopentenone (**1b**) underwent the asymmetric addition of phenyl- and 1-heptenylboronic acids with high enantioselectivity under the same reaction conditions to give 3-substituted cyclopentanones **3bm** (97% ee (*S*)) (entry 6) and **5bm** (96% ee) (entry 12), in high yields. High enantioselectivities were also observed in the reaction of linear enones **1d** and **1e**, which have *trans* olefin geometry (entries 8 and 9). Thus, the rhodium-catalyzed asymmetric con-









entry	enone 1	boronic acid 2 or 4 (eq to 1)	ketone 3 or 5 yield (%)	% ee
1	1a	2m (5.0)	3am >99	97 (S)
2	1a	2n (5.0)	3an >99	97
3[a]	1a	2o (2.5)	3ao 70	99
4	1a	2p (5.0)	3ap 97	96
5	1a	2q (5.0)	3aq 94	96
6	1b	2m (1.4)	3bm 93	97 (S)
7	1c	2m (1.4)	3cm 51	93
8	1d	2m (5.0)	3dm 82	97
9	1e	2m (2.5)	3em 88	92
10	1a	4m (2.5)	5am 88	94
11	1a	4n (5.0)	5an 76	91
12	1b	4m (2.5)	5bm 64	96

[a] In 1-propanol/H_2O (10/1).

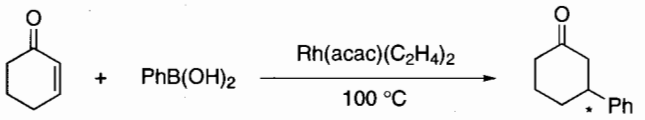
Scheme 4.2 Asymmetric conjugate addition of organoboronic acids to α,β-unsaturated ketones catalyzed by Rh(acac)$(C_2H_4)_2$/(*S*)-binap.

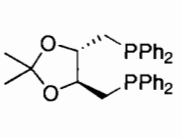
jugate addition proceeds with high enantioselectivity for both cyclic and linear α,β-unsaturated ketones with various aryl- and alkenylboronic acids.

The change of rhodium precursor from Rh(acac)$(CO)_2$ to Rh(acac)$(C_2H_4)_2$ is of crucial importance for the high yield and high enantioselectivity. The use of Rh(acac)$(CO)_2$ in place of Rh(acac)$(C_2H_4)_2$ under the same conditions for the reaction of 2-cyclohexenone (**1a**) with phenylboronic acid (**2m**) resulted in a much lower yield and only 43% enantioselectivity. This is explained by incomplete formation of the catalytically active species, namely Rh(acac)((*S*)-binap), because of the stronger coordination ability of carbon monoxide to rhodium than that of ethylene. In this reaction, a major problem is the rhodium-catalyzed protodeboronation of organoboronic acid as a competing side reaction. As a result, a large excess of organoboronic acids (**1.4–5.0** equiv to enones) were used to achieve high yields.

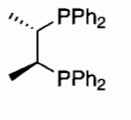
After the initial report by Hayashi and Miyaura [3], several other chiral ligands were examined for their enantioselectivity in the asymmetric conjugate addition under similar reaction conditions. Scheme 4.3 summarizes some of the results. With diop, chiraphos, *ip*-phox or bppfa, the reaction gave much lower enantioselectivity and the yields were also poor [4]. Enantioselectivities as high as that obtained with binap, along with high yields, were observed with L-proline-based amidomonophosphine **6** [5], H_8-monophos **7** [6], binaphthol-based diphosphonite **8** [7], (*R*)-digm-binap **9** [8], bipyridyl-based diphosphine **10** [9], dicyclophane imidazolium carbene **11** [10], and norbornadiene-based chiral diene **12** [11]. Especially notable is the 13 200 turnover number achieved in the reaction with the (*R*)-digm-binap (**9**) ligand. This result shows the potential for industrial-scale application of this asymmetric reaction.

In place of organoboronic acids, several other organoboron compounds can be used for the asymmetric conjugate addition (Figure 4.1). They have some advantages over others. (1) Because organoboronic acids are readily subject to cyclic trimerization with loss of water to form organoboroxines; it is usually difficult to determine the exact stoichiometry of the organoboronic acids. The use of more stable organoboroxines (**13**), which have similar reactivity to organoboronic acids, can avoid this problem. (2) Alkenylcatecholborane **14** is a good reagent for conjugate addition and is easily obtained by the hydroboration of an alkyne with catecholborane. One-pot asymmetric synthesis of the conjugate addition product, β-alkenyl ketone, is possible starting from an alkyne and catecholborane without isolation of the alkenylcatecholborane [12]. (3) Lithium trimethyl arylborate **15** is also a good reagent for asymmetric conjugate addition. It is readily generated in situ by treatment of an aryl bromide with butyllithium and trimethoxyborane, and in some cases it has a higher activity than the corresponding organoboronic acid [13]. (4) Potassium organotrifluoroborate **16** is generally more stable than the corresponding organoboronic acid. As a typical example, an unsubstituted vinyl group can be introduced with high enantioselectivity in high yield by use of the vinyltrifluoroborate. The corresponding boronic acid cannot be used because of its instability under the reaction conditions [14]. (5) Bis(pinacolato)diboron (**17**) and bis(neopentyl glycolate)diboron (**18**) have been used for the rhodium-catalyzed conjugate addition to α,β-unsaturated ketones, giving β-boryl ketones, though the asymmetric version has not been reported [15].

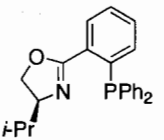




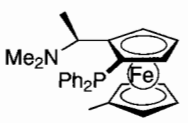
(*S*,*S*)-diop
24% ee (*S*)



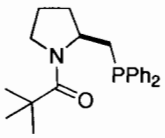
(*S*,*S*)-chiraphos
40% ee (*S*)



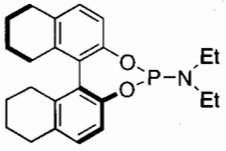
(*S*)-*ip*-phox
0% ee



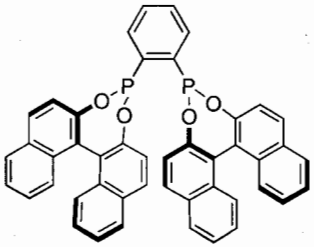
(*S*)-(*R*)-bppfa
3% ee (*S*)



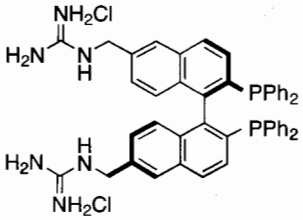
6
96% ee (*S*)



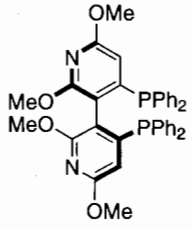
7 (*S*)-H_8-monophos
>98% ee (*S*)



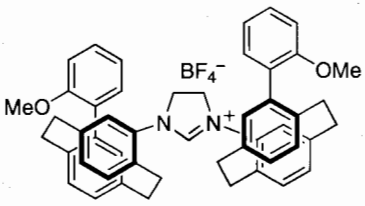
8
99% ee (*S*)



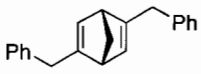
9 (*R*)-*digm*-binap
98% ee (*R*)



10 (*S*)-P-phos
99% ee



11
98% ee



12
96% ee (*R*)

Scheme 4.3 Asymmetric conjugate addition catalyzed by chiral ligand rhodium complexes.

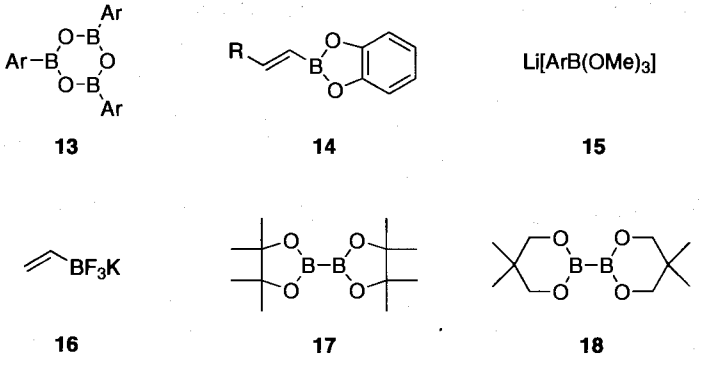
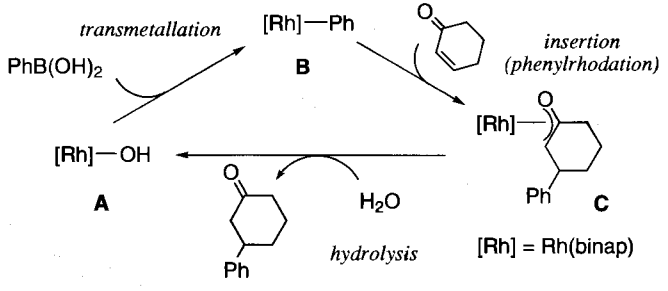


Figure 4.1 Organoboron compounds used for the rhodium-catalyzed conjugate addition.

4.3 Mechanism

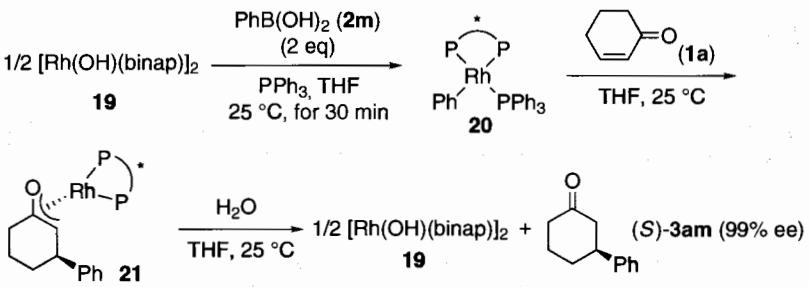
In 2002, the catalytic cycle of the asymmetric conjugate addition was established by Hayashi and co-workers [16]. An example is given for the reaction of phenylboronic acid (**2m**) with 2-cyclohexenone (**1a**) in Scheme 4.4. The reaction has three main intermediates, hydroxorhodium **A**, phenylrhodium **B**, and oxa-π-allylrhodium **C** complexes that are related in the catalytic cycle as follows (1) transmetallation of a phenyl group from boron to hydroxorhodium **A**, giving phenylrhodium **B**, (2) insertion of 2-cyclohexenone into the phenyl–rhodium bond of phenylrhodium **B**, forming oxa-π-allylrhodium **C**, and (3) hydrolysis of **C** giving the conjugate addition product and regenerating hydroxorhodium **A**.



Scheme 4.4 Catalytic cycle for the rhodium-catalyzed conjugate addition.

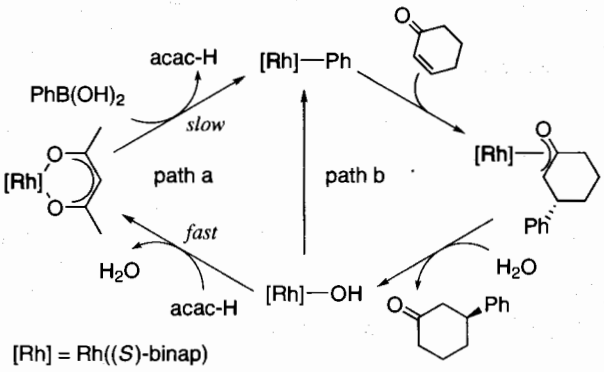
Hayashi proved the validity of this catalytic cycle by observing all three intermediates and transformations in NMR experiments [16] (Scheme 4.5). Transmetallation of a phenyl group from boron to rhodium takes place by addition of phenylboronic acid (**2m**) to hydroxorhodium complex **19** in the presence of triphenylphosphine to gen-

erate the phenylrhodium intermediate **20**. This intermediate then reacts with 2-cyclohexenone (**1a**) to give oxa-π-allylrhodium **21**, which is converted immediately into hydroxorhodium complex **19** on addition of water, liberating the phenylation product **3am**. In this NMR study, triphenylphosphine was used to stabilize the phenylrhodium(I) complex. In the absence of triphenylphosphine, the characterization of the phenyl–rhodium species was unsuccessful.



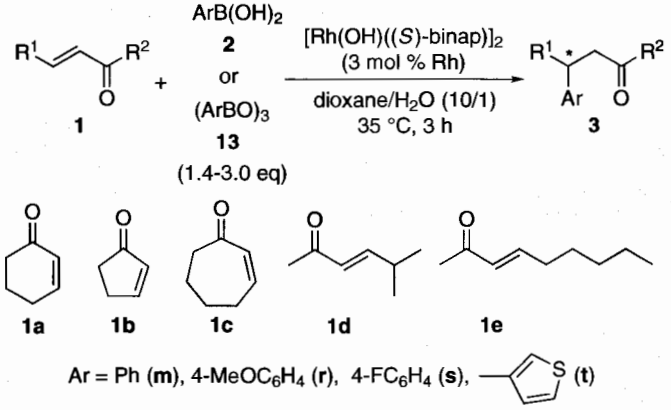
Scheme 4.5 Reactions of rhodium binap complex.

These NMR experiments brought great insight into the catalytic reaction. While a high reaction temperature, normally 100 °C, is required in the catalytic reaction, all three transformations in Scheme 4.5 were found to proceed independently at 25 °C. In the same paper [16], Hayashi et al. demonstrated why the catalytic reaction does not take place at such a lower temperature. An outline of the reason is shown in Scheme 4.6. In the catalytic reaction, Rh(acac)(binap) is involved as another significant intermediate because Rh(acac)(C_2H_4)$_2$ is used as rhodium precursor. It was confirmed that the hydroxorhodium complex is immediately converted into the Rh(acac)(binap) by reaction with 1 equiv of acetylacetone at 25 °C, and the transmetallation from boron to rhodium is very slow at the same temperature for the Rh(acac)(binap) complex. Thus, the acetylacetonato ligand inhibits the catalytic reaction (Scheme 4.6, path a).



Scheme 4.6 Catalytic cycle for the conjugate addition catalyzed by a rhodium acetylacetonato complex.

On the basis of this finding, [Rh(OH)(binap)]$_2$, an acetylacetonato-free rhodium complex, was tested as a catalyst (Scheme 4.6, path b). As expected, the conjugate addition took place at a lower temperature (Scheme 4.7). For example, the addition of phenylboronic acid (**2m**) or phenylboroxine (**13m**) to 2-cyclohexenone (**1a**) is catalyzed by [Rh(OH)(binap)]$_2$ at 35 °C to give a quantitative yield of **3am** with 99.3% ee. This catalytic system is also applicable to the reaction of other enones and organoboron reagents. Because the reaction temperature is lower, the enantioselectivity is always higher than that observed in the reaction catalyzed by the rhodium-acac complex at 100 °C. Chemical yields are higher even when using a lower amount of the boron reagents because the protodeboronation of the boronic acids, which is the main side reaction, is suppressed at lower temperatures. The higher efficiency of



entry	enone 1	2 or 13 (eq to 1)	ketone 3	yield (%)	% ee	
1	**1a**	**2m** (2.5)	**3am**	96	99	(*S*)
2	**1a**	**13m** (2.5)	**3am**	98	99.3	(*S*)
3	**1a**	**13m** (1.4)	**3am**	94	99.2	(*S*)
4	**1a**	**13r** (2.5)	**3ar**	96	99.1	
5	**1a**	**13s** (2.5)	**3as**	96	99.1	
6	**1b**	**13m** (2.5)	**3bm**	95	98	(*S*)
7	**1c**	**13m** (2.5)	**3cm**	94	96	(*S*)
8	**1d**	**13m** (2.5)	**3dm**	89	98	(*S*)
9	**1e**	**13m** (2.5)	**3em**	92	98	(*R*)
10[a]	**1a**	**2t** (3.0)	**3at**	67	99	(*S*)
11[a]	**1b**	**2t** (3.0)	**3bt**	78	97	(*S*)
12[a]	**1c**	**2t** (3.0)	**3ct**	81	99	(*S*)
13[a]	**1d**	**2t** (3.0)	**3dt**	75	99	(*S*)

[a] At 40 °C for 24 h.

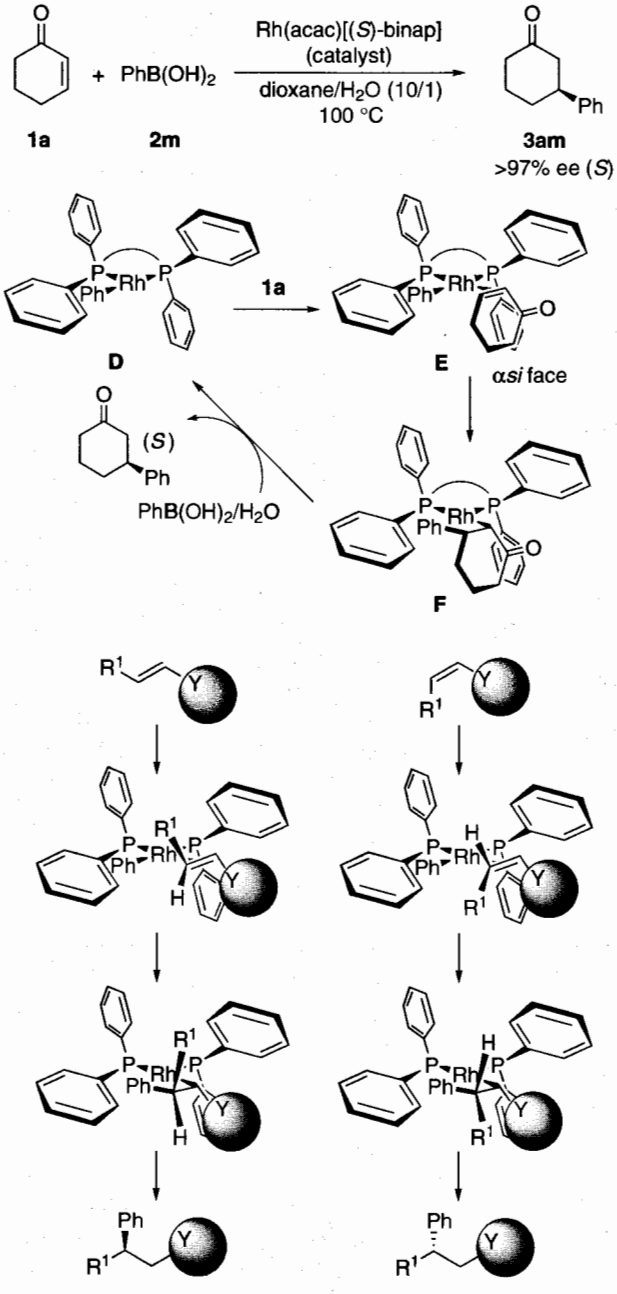
Scheme 4.7 Asymmetric conjugate addition catalyzed by [Rh(OH)((*S*)-binap)]$_2$.

the [Rh(OH)(binap)]$_2$ catalyst was also observed in the asymmetric addition of 3-thiopheneboronic acid (**2t**) to enones [17] (Scheme 4.7).

Scheme 4.8 shows the stereochemical pathway in the reaction catalyzed by the rhodium complex coordinated with (*S*)-binap. According to the highly skewed structure known for transition metal complexes coordinated with a binap ligand [18], (*S*)-binap–rhodium intermediate **D** should have an open space at the lower part of the vacant coordination site, the upper part being blocked by one of the phenyl rings of the binap ligand. The olefinic double bond of 2-cyclohexenone (**1a**) coordinates to rhodium with its α*si* face, forming **E**, which undergoes migratory insertion to form a stereogenic carbon center in **F** whose absolute configuration is *S*. Absolute configurations of all the conjugate addition products can be predicted by this type of stereochemical model: (*S*)-binap–rhodium intermediate attacking the α*si* face of α,β-unsaturated ketones, both cyclic and linear ones, and other electron deficient olefins, including α,β-unsaturated esters and alkenylphosphonates (vide infra).

The catalytically active rhodium complex [Rh(OH)(binap)]$_2$ can also be prepared in situ by mixing a rhodium halide and an inorganic base, e.g. the combination of [RhCl(binap)]$_2$ and KOH. Thus, the role of inorganic bases is to convert rhodium halide into hydroxorhodium. However, very recently, Miyaura and co-workers reported an additional effect of the bases in accelerating the reaction [19]. Reactions performed with a combination of hydroxorhodium and a base were faster than those only with hydroxorhodium. The role of the base was considered to be quaternization of the boronic acid, to facilitate its transmetallation to the hydroxorhodium, or assistance of hydrolysis of a rhodium enolate intermediate. This combination enables the reaction to be carried out even at room temperature. However, for the asymmetric reaction, it must be kept in mind that procedures using inorganic bases often suffer from low enantioselectivity in return for a faster reaction [8, 19]. This is presumably caused by formation of a phosphine-free rhodium species by coordination of the inorganic base to the rhodium metal center.

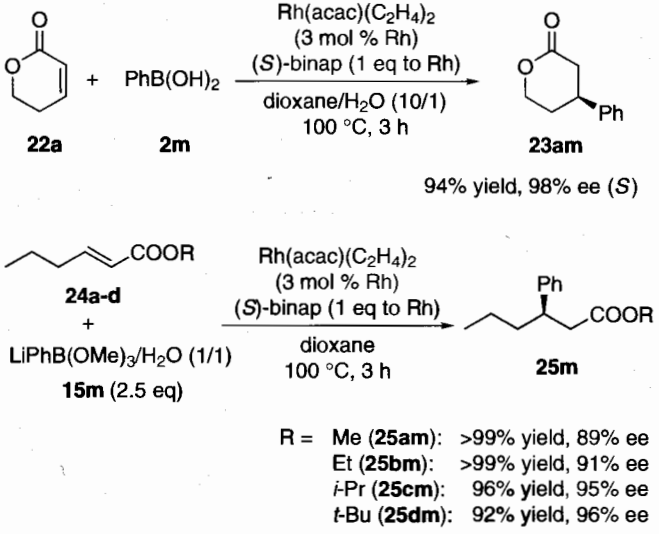
Miyaura also reported that a rhodium complex coordinated with 1,5-cyclooctadiene (cod) is a highly active catalyst for the rhodium-catalyzed conjugate addition [20]. This reaction featured the addition of *p*-tolylboronic acid to methyl vinyl ketone in the presence of [RhCl(cod)]$_2$ in neat water at 100 °C. The corresponding conjugate addition product was obtained in 46 000 turnover number (TON). These phosphine-free condition gave a 24 000 TON for the addition of *p*-tolylboronic acid to 2-cyclohexenone [21]. These results indicate that the generation of a chiral phosphine-rhodium catalyst by mixing a rhodium-cod precursor with a chiral phosphine ligand may cause lower enantioselectivity if the ligand exchange is incomplete. Therefore, asymmetric reactions are usually carried out with an isolated chiral phosphine-rhodium catalyst or a combination of a chiral phosphine and a more labile bis(ethylene)rhodium precursor. Alternatively, a solution of a chiral phosphine and a rhodium-cod precursor is heated for a while before addition of the starting materials.



Scheme 4.8 Proposed stereochemical pathway in the conjugate addition catalyzed by rhodium (*S*)-binap complex.

4.4
Addition of Organoboronic Acids to Other Alkenes

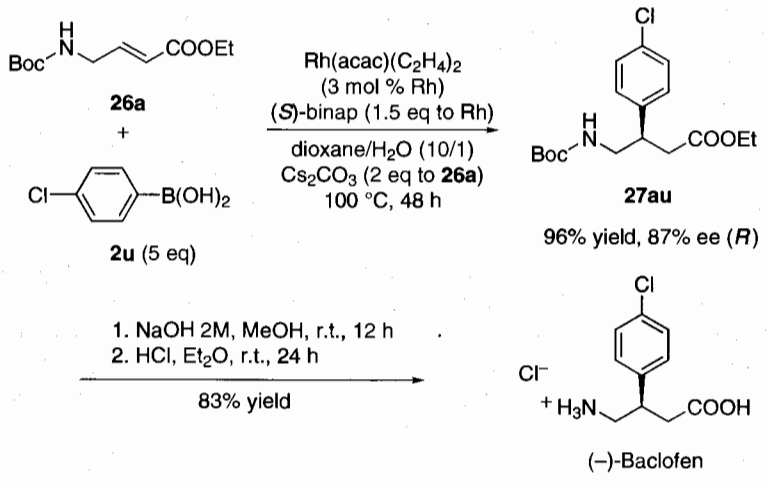
Rhodium-catalyzed asymmetric conjugate addition is applicable to α,β-unsaturated esters (Scheme 4.9). Hayashi and co-workers reported [22] that the reaction of 5,6-dihydro-2*H*-pyran-2-one (**22a**) with phenylboronic acid gave a 94% yield of phenylated lactone (*S*)-**23am** with 98% ee. For the linear enoates, organoboronic acids did not give high yields of the addition products. Much better results were obtained with the lithium arylborates **15**, which are generated in situ from aryl bromides, butyllithium, and trimethoxyborane. Enantioselectivity is higher with the sterically bulkier ester groups, though the yields decrease as the steric bulkiness increases. The results are explained by the molecular recognition model shown in Scheme 4.8. Similar results for the asymmetric conjugate addition to α,β-unsaturated esters have been reported independently by Miyaura and co-workers [23].



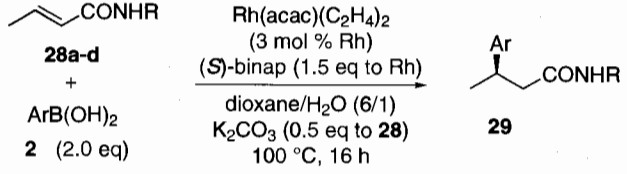
Scheme 4.9 Asymmetric conjugate addition of organoboron reagents to α,β-unsaturated esters.

Asymmetric addition of 4-chlorophenylboronic acid (**2u**) to α,β-unsaturated γ-amino ester (**26a**), followed by deprotection and ester hydrolysis gave optically active 4-amino-3-(4-chlorophenyl)butyric acid (Baclofen) hydrochloride (Scheme 4.10), which plays an important role in various nervous system functions. The best result was observed with a large excess of organoboronic acids (5.0 equiv to **26a**) in a 10:1 dioxane–water mixture containing aqueous cesium carbonate [24].

α,β-Unsaturated amides **28** were less reactive than the enones or enoates under the standard conditions (entry 1 in Scheme 4.11). Sakuma and Miyaura found [25] that the conjugate addition is accelerated by the addition of potassium carbonate. The enantioselectivity is comparable to that of additions to the corresponding esters.



Scheme 4.10 Enantioselective synthesis of (–)-Baclofen, using asymmetric conjugate addition of boronic acid **2u** to α,β-unsaturated ester **26a**.



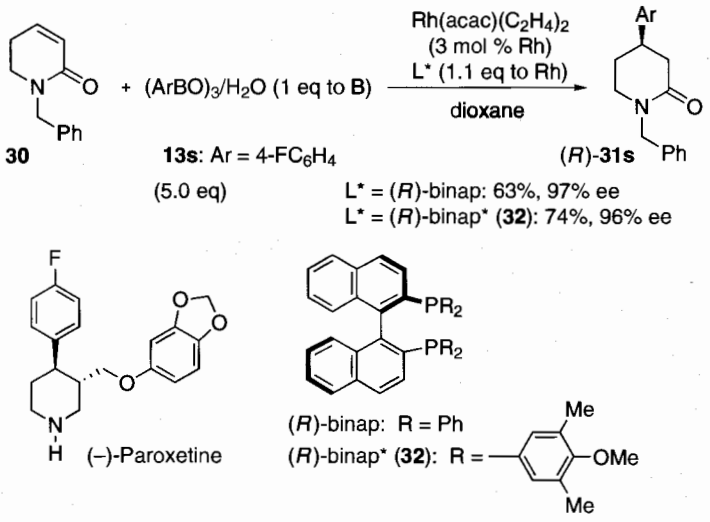
R = CH_2Ph (**28a**), *c*-Hex (**28b**), H (**28c**), Ph (**28d**)
Ar = Ph (**2m**), 4-MeC_6H_4 (**2n**), 4-$CF_3C_6H_4$ (**2o**), 4-$MeOC_6H_4$ (**2r**)

entry	amide **28**	boronic acid **2**	amide **29**	yield (%)	% ee
1[a]	**28a**	**2m**	**29am**	67	93 (*R*)
2	**28a**	**2m**	**29am**	85	93 (*R*)
3	**28b**	**2m**	**29bm**	89	93
4	**28c**	**2m**	**29cm**	62	89
5	**28d**	**2m**	**29dm**	88	90
6	**28a**	**2n**	**29an**	74	87
7	**28a**	**2o**	**29ao**	82	92
8	**28a**	**2s**	**29as**	50	77

[a] Without K_2CO_3.

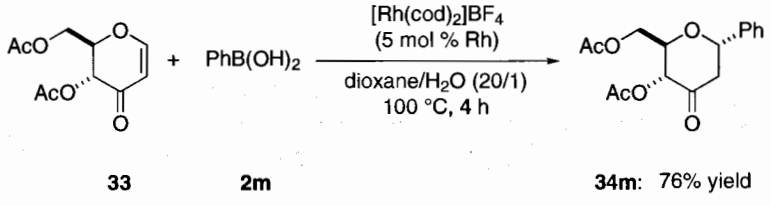
Scheme 4.11 Asymmetric conjugate addition of organoboronic acids to α,β-unsaturated amides.

Asymmetric addition to cyclic α,β-unsaturated amides gave optically active 4-(4-fluorophenyl)-2-piperidinone **31s**, which is a key intermediate for the synthesis of biologically active compounds such as Paroxetine [26] (Scheme 4.12). Because the protodeboronation of boronic acids **2s** was a serious side reaction in this case, slightly modified conditions were required. Thus, the reaction of lactam **30** with 4-fluorophenylboroxine (**13s**) and 1 equiv (to boron) of water in the presence of Rh(acac)$(C_2H_4)_2$/(*R*)-binap catalyst in dioxane at 40 °C gave 63% yield of (*R*)-**31s** with 97% enantioselectivity. The use of boroxine **13s** and 1 equiv of water is a key factor for the success of this reaction. This is much better than the reaction carried out with the corresponding boronic acid under the usual conditions. Thus, when the reaction is conducted at 100 °C in the presence of a large excess of water as co-solvent, the yield of **31** is only 17%. The use of the modified binap ligand containing 3,5-dimethyl-4-methoxyphenyl groups on the phosphorus atoms (binap*, **32**) gave a higher yield of **31**.



Scheme 4.12 Asymmetric conjugate addition to cyclic α,β-unsaturated amides.

Maddaford and co-workers have reported the diastereoselective synthesis of *C*-glycoside **34m** by use of rhodium-catalyzed conjugate addition [27] (Scheme 4.13). The reaction is efficiently catalyzed by cationic rhodium catalysts such as [Rh(cod)$_2$]BF_4,



33 **2m** **34m**: 76% yield

Scheme 4.13 Diastereoselective conjugate addition to enone **33**.

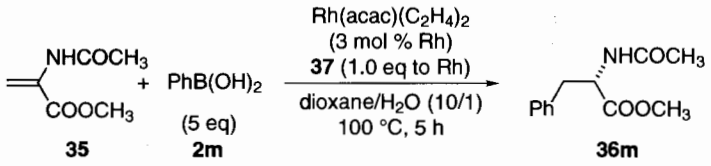
and the addition of phosphine ligands inhibited the conjugate addition. It is likely that the enone **33** derived from the pyranose is less reactive toward the conjugate addition.

An interesting asymmetric transformation, reported by Reetz et al., is the asymmetric conjugate addition of phenylboronic acid to α-acetamidoacrylic ester **35**, giving phenylalanine derivative **36m** [7] (Scheme 4.14). The addition of phenylboronic acid (**2m**) in the presence of a rhodium complex of 1,1′-binaphthol-based diphosphinite ligand **37** gave a quantitative yield of **36** in up to 77% ee. In this asymmetric reaction, the stereochemical outcome is determined at the hydrolysis step of an oxa-π-allylrhodium intermediate, not at the insertion step (cf. Scheme 4.8). Similar rhodium-catalyzed conjugate additions of arylboronic acids to α,β-dehydroamino acid derivatives have also been reported by Frost and co-workers [28]. Very recently, Darses and Genet reported an efficient strategy for this asymmetric reaction, where 2-methoxyphenol was employed as a proton source in place of water [29]. While the reaction of α-acetamidoacrylic ester **35** and potassium phenyltrifluoroborate **16m** catalyzed by $[Rh(cod)_2]PF_6$/(*R*)-binap (1.1 eq to Rh) in the presence of water gave only 16% ee of the product **36m**, the reaction in the presence of 2-methoxyphenol gave 83% ee of **36m**. A slight improvement in the ee value (90% ee) was obtained by using 2.2 equiv of (*R*)-binap ligand to $[Rh(cod)_2]PF_6$. This result is probably due to incomplete ligand exchange, leaving $[Rh(cod)_2]PF_6$, which may have an activity for the reaction (Section 4.3). Using phenylboronic acid (**2m**) instead of **16m** led to a lower ee (42% ee), possibly because boronic acids might act as a competitive proton source.

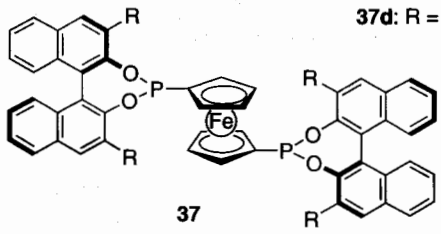
In the asymmetric addition to alkenylphosphonate **38** [30] (Scheme 4.15), the yield depends on the amount of water added to the reaction. The combination of boroxine and 1 equiv (to boron) of water gave a high yield of the desired product **39m** with 96% ee. Alkylphosphonate **39** was used as a chiral building block for the synthesis of optically active alkenes by a Horner–Emmons-type reaction.

A nitroalkene is another good substrate for the rhodium-catalyzed asymmetric conjugate addition of organoboronic acids [31]. In this study, Hayashi et al. reported that the reaction of 1-nitrocyclohexene (**40**) with phenylboronic acid (**2m**) in the presence of the rhodium/(*S*)-binap catalyst at 100 °C for 3 h gave 89% yield of 2-phenyl-1-nitrocyclohexane (**41m**) (Scheme 4.16). The main phenylation product **41m** is a *cis* isomer (*cis*:*trans* = 87:13) and both the *cis* and *trans* isomers are 98% enantiomerically pure. Treatment of the *cis*-isomer with sodium bicarbonate in refluxing ethanol caused epimerization, giving the thermodynamically more stable *trans* isomer (*trans*:*cis* = 97:3). Optically active nitroalkanes obtained by this method are useful chiral building blocks that can be readily converted into a wide variety of optically active compounds by taking advantage of the versatile reactivity of nitro compounds.

Lautens et al. reported the rhodium-catalyzed addition of arylboronic acids to vinyl-substituted nitrogen heteroaromatic compounds [32]. The reaction of 2-vinylpyridine (**42a**) with phenylboronic acid (**2m**) and $[RhCl(cod)]_2$/TPPDS catalyst in the presence of sodium carbonate and sodium dodecyl sulfate (SDS) as a phase-transfer agent in water at 80 °C for 15 h gave a 84% yield of the addition product **43am** (Scheme 4.17). The water-soluble TPPDS was a ligand of choice to help dissolve the catalyst in water. Under these conditions, the addition of arylboronic acids was also observed for sev-



L* = **37a**: R = H 67 %ee
37b: R = CH_3 55 %ee
37c: R = Br 70 %ee
37d: R = Ph 77 % ee (3 eq NaF)



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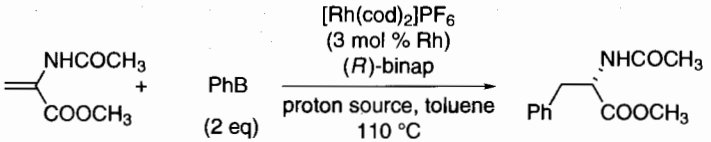
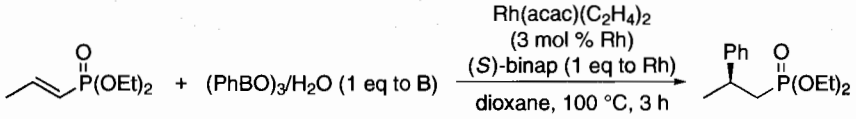


proton souce	PhB	(*R*)-binap	yield	ee
H_2O	$PhBF_3K$ (**16m**)	1.1 eq to Rh	quant.	16%
2-methoxyphenol	$PhBF_3K$ (**16m**)	1.1 eq to Rh	91%	83%
2-methoxyphenol	$PhBF_3K$ (**16m**)	2.2 eq to Rh	89%	90%
2-methoxyphenol	$PhB(OH)_2$ (**2m**)	2.2 eq to Rh	42%	42%

Scheme 4.14 Rhodium-catalyzed asymmetric conjugate addition giving phenylalanine.

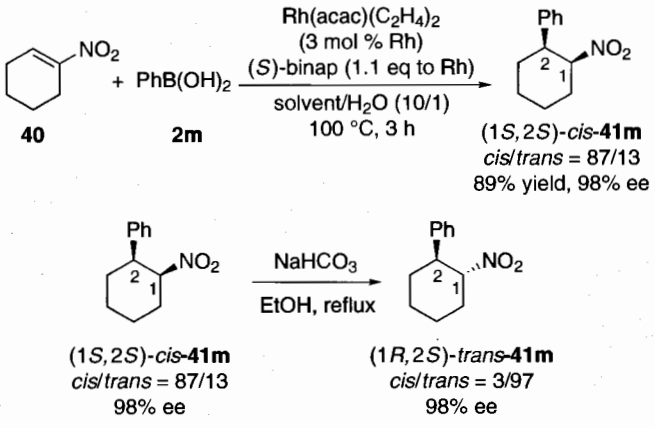


94% yield, 96% ee (*S*)

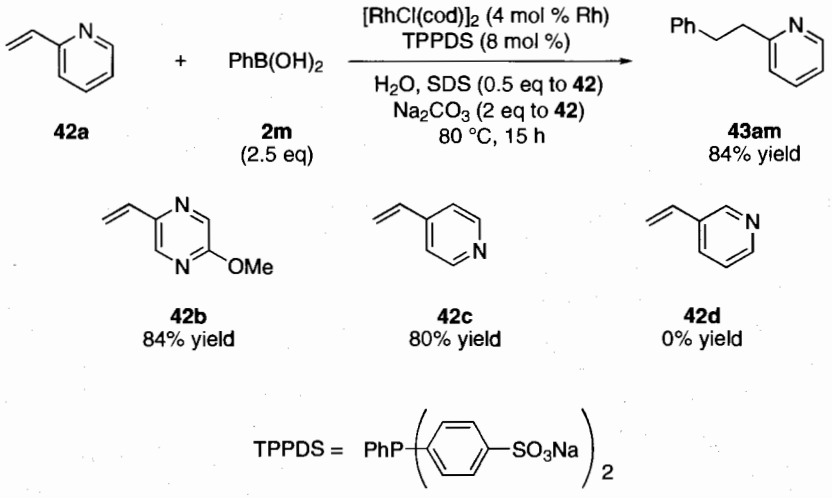
Scheme 4.15 Catalytic asymmetric conjugate addition to propenylphosphonate **38**.

eral other vinyl-substituted nitrogen heteroaromatic compounds, such as **2**-vinylpyrazole **42b** or 4-vinylpyridine (**42c**). One exception was, however, 3-vinylpyridine (42d), which did not react. The reaction mechanism is probably similar to that of the conjugate addition (Section 4.3)

In contrast with the vinyl nitrogen heteroaromatic compounds, styrenyl olefins gave Heck-type products under exactly the same reaction conditions. *trans*-Stilbene



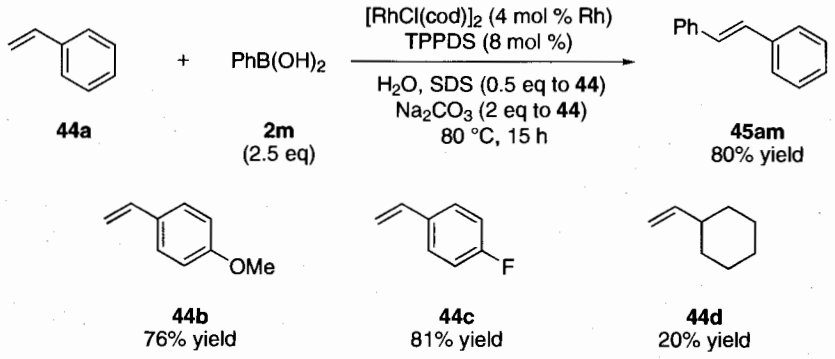
Scheme 4.16 Catalytic asymmetric conjugate addition to nitrocyclohexene **40**.



Scheme 4.17 Rhodium-catalyzed addition of arylboronic acids to vinyl-substituted nitrogen heteroaromatic compounds.

(**45am**) was formed in 80% yield in the reaction of styrene (**44a**) with phenylboronic acid (**2m**) (Scheme 4.18). The reaction of 4-methoxystyrene (**44b**) or 4-fluorostyrene (**44c**) gave Heck-type products analogously. Even aliphatic olefin **44d** gave the corresponding product, though the yield was low due to olefin isomerization.

With α,β-unsaturated esters, a similar rhodium-catalyzed Heck-type reaction of arylboronic acids was reported by Zou et al. [33]. *t*-Butyl acrylate (**46a**) reacted with phenylboronic acid (**2m**) in the presence of the $RhCl_3(H_2O)_3$, which is a rhodium precursor of choice, and PPh_3 in a 3:1 toluene–water mixture at 100 °C for 20 h to give a 83% yield of *trans*-cinnamate (**47am**) (Scheme 4.19). The reaction of methyl acrylate

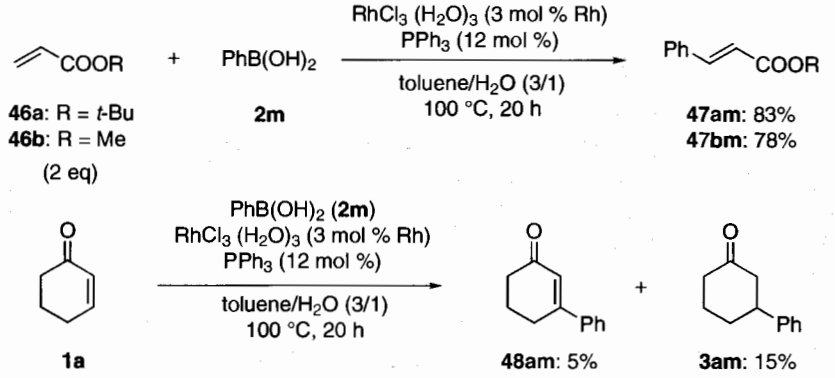


44a + **2m** (2.5 eq) → **45am** 80% yield

44b 76% yield **44c** 81% yield **44d** 20% yield

Scheme 4.18 Rhodium-catalyzed Heck-type reaction of styrenes with organoboronic acids.

(**46b**) also proceeded, in 78% yield, to give the Heck-type product. However, these reactions are limited to those of monosubstituted olefins. Under the same reaction conditions, disubstituted olefins such as 2-cyclohexenone (**1a**) gave Heck-type products in low yield, accompanied by the formation of the 1,4-addition product **3am**.



46a: R = *t*-Bu
46b: R = Me
(2 eq)

2m

47am: 83%
47bm: 78%

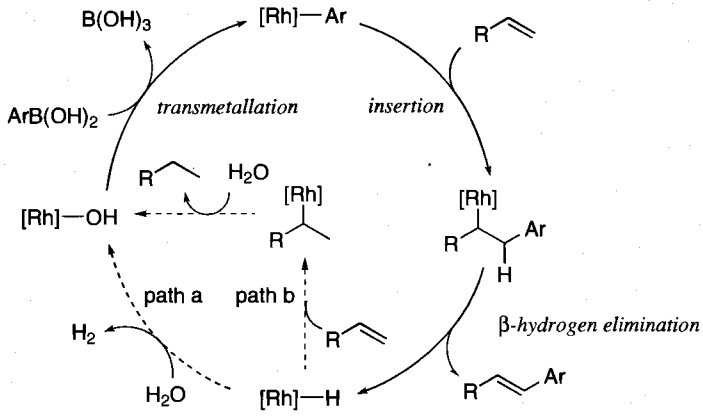
1a

48am: 5% + **3am**: 15%

Scheme 4.19 Rhodium-catalyzed Heck-type reaction of α,β-unsaturated olefins with organoboronic acids.

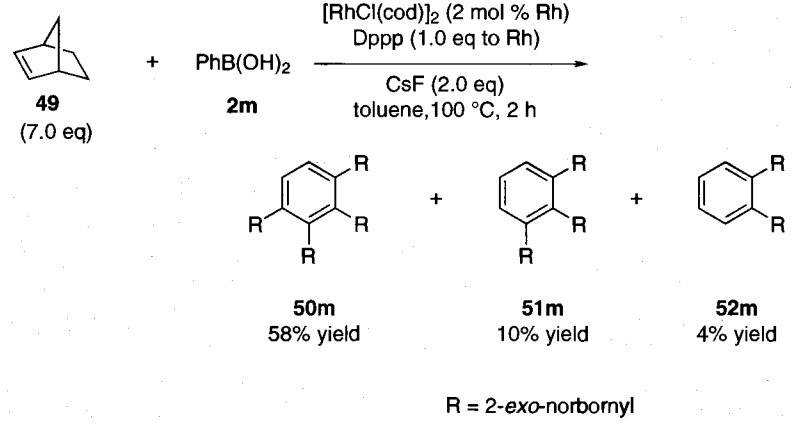
Scheme 4.20 shows the proposed catalytic cycle of these Heck-type reactions. Insertion of arylrhodium complex with an olefin gives an alkylrhodium intermediate. This is followed by β-hydrogen elimination to give a hydridorhodium species, liberating the Heck-type product. We should consider at this point that the hydridorhodium species can undergo several possible pathways to regenerate the phenylrhodium complex. One possibility is that the hydridorhodium species could be converted into a hydroxorhodium complex on addition of water (path a). Then, transmetallation of an aryl group from boron to the hydroxorhodium regenerates the arylrhodium intermediate. Another possibility is that a sacrificial starting olefin might insert into the hydridorhodium to give an alkylrhodium or a rhodium enolate intermediate (path b), followed by hydrolysis regenerating the hydroxorhodium complex. It is also possible

that the arylboronic acid acts as a protonolysis source. Although not proven, the formation of hydridorhodium species and its hypothetical conversion into the arylrhodium intermediate are of particular interest in this field. These mechanistic aspects should be supported with clear evidence.



Scheme 4.20 Proposed catalytic cycle for the rhodium-catalyzed Heck-type reaction of olefins with organoboronic acids.

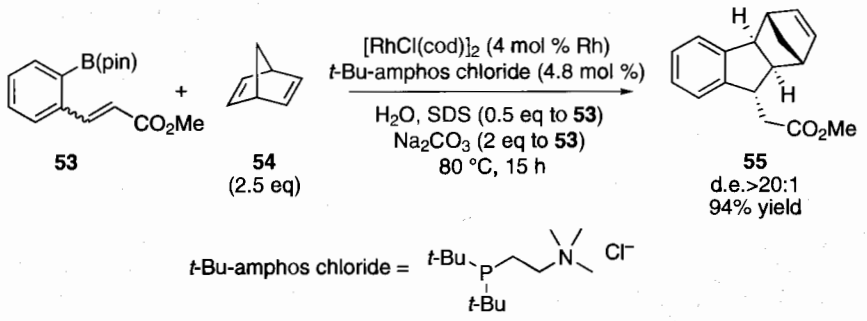
Miura and co-workers have reported a rhodium-catalyzed multiple alkylation of phenylboronic acid [34]. The reaction of a large excess of 2-norbornene (**49**) with phenylboronic acid (**2m**) in the presence of the $[RhCl(cod)]_2$/dppp catalyst in toluene gave a mixture of 1,2,3,4-tetra- (**50m**), 1,2,3-tri- (**51m**), and 1,2-di(2-norbornyl)benzenes (**52m**) (Scheme 4.21).



Scheme 4.21 Rhodium-catalyzed multiple alkylation of phenylboronic acid.

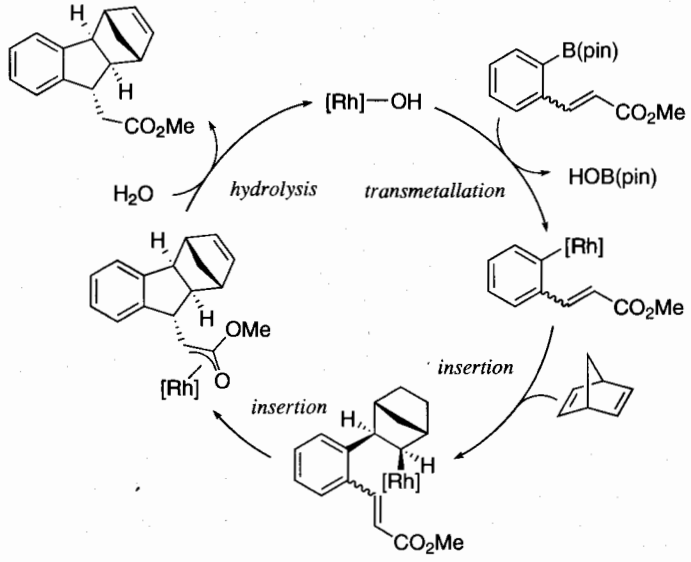
Lautens and Mancuso reported a rhodium-catalyzed tandem carbocyclization of arylboronate esters bearing a pendant Michael-acceptor alkene with norbornene de-

rivatives, which formed indanes diastereoselectively [35]. As an electron-rich and bulky water-soluble phosphine ligand, *t*-Bu-amphos chloride was used along with [RhCl(cod)]$_2$ catalyst in water. The reaction of pinacolboronate ester **53** with norbornadiene (**54**) and [RhCl(cod)]$_2$/*t*-Bu-amophos chloride catalyst in the presence of sodium carbonate and sodium dodecyl sulfate (SDS) as a phase transfer agent in water at 80 °C for 15 h gave a 94% yield of the indane derivative **55** (Scheme 4.22).



Scheme 4.22 Diastereoselective formation of indanes via rhodium-catalyzed tandem carbocyclization.

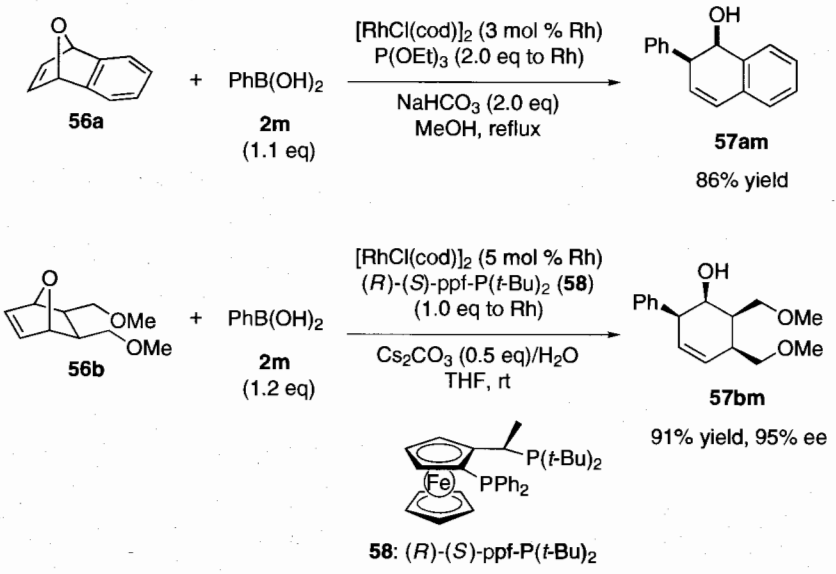
The proposed catalytic cycle is described in Scheme 4.23. Transmetallation of arylboronate esters to hydroxorhodium species, giving an arylrhodium intermediate, is followed by insertion of the norbornene derivative. Then, the alkylrhodium intermediate, which has no hydrogens for β-hydrogen elimination, undergoes insertion of



Scheme 4.23 Proposed catalytic cycle for the rhodium-catalyzed diastereoselective formation of indanes.

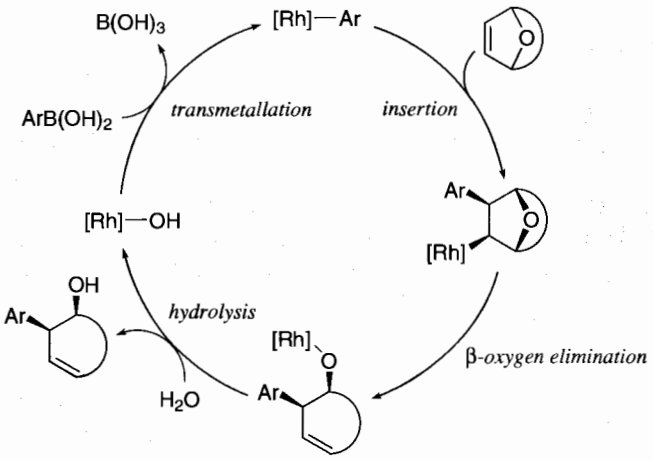
the internal pendant olefin to form an oxa-π-allylrhodium intermediate. Its hydrolysis gives the tandem carbocyclized product and regenerates the active hydroxorhodium species. Importantly, it is remarkable that the insertion of the internal olefin into rhodium–sp^3 carbon takes place in this catalytic cycle, because no examples of rhodium-catalyzed addition of alkyl groups to olefins had been reported previously.

Rhodium-catalyzed addition of arylboronic acids to oxanorbornenes was independently reported by the groups of Murakami [36] and Lautens [37] (Scheme 4.24). Murakami reported that the reaction of oxabenzonorbornadiene (**56a**) with phenylboronic acid (**2m**), in the presence of a rhodium/$P(OEt)_3$ catalyst in MeOH at reflux, gave a 86% yield of the ring-opened alcohol **57am**. Lautens reported the asymmetric version of this reaction, and a high enantioselectivity was observed with chiral ferrocenylbisphosphine ligand **58** in a THF solution containing aqueous cesium carbonate. For example, [2.2.1]oxabicycle **56b** reacted with phenylboronic acid (**2m**) to give the ring-opened alcohol **57bm**, whose enantiomeric purity is 95%. The catalytic cycle was proposed to involve β-oxygen elimination as a key step (Scheme 4.25). Thus, insertion of the double bond of oxanorbornene into the aryl–rhodium bond forms an alkylrhodium intermediate, which undergoes β-oxygen elimination to give an alkoxyrhodium intermediate. Then, hydrolysis and transmetallation regenerates the arylrhodium intermediate. The stereochemical outcome of the asymmetric reaction is determined at the enantioposition-selective carborhodation of the meso-type alkene.



Scheme 4.24 Rhodium-catalyzed asymmetric addition of phenylboronic acid to oxanorbornenes.

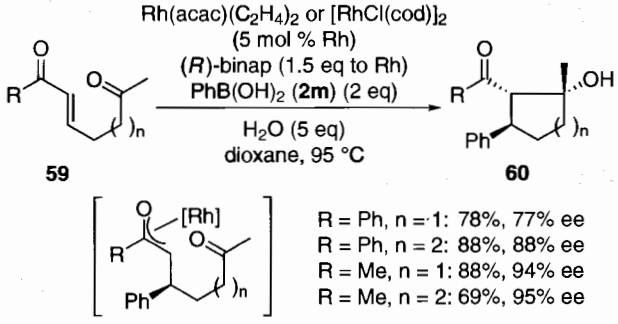
Very recently, Hayashi and co-workers reported a catalytic asymmetric conjugate addition forming chiral boron enolates by use of 9-phenyl-9-borabicyclo[3.3.1]nonane (*B*-Ph-9BBN) as an organoboron reagent, which proceeds in an aprotic solvent [38].



Scheme 4.25 Proposed catalytic cycle for the rhodium-catalyzed addition of organoboronic acids to oxanorbornenes.

The boron enolates (up to 98% ee) were used for further transformation by treatment with electrophiles. The rhodium-catalyzed reaction of *B*-Ph-9BBN was extended to a new type of catalytic tandem conjugate addition–aldol reaction by combination with vinyl ketones and aldehydes [39].

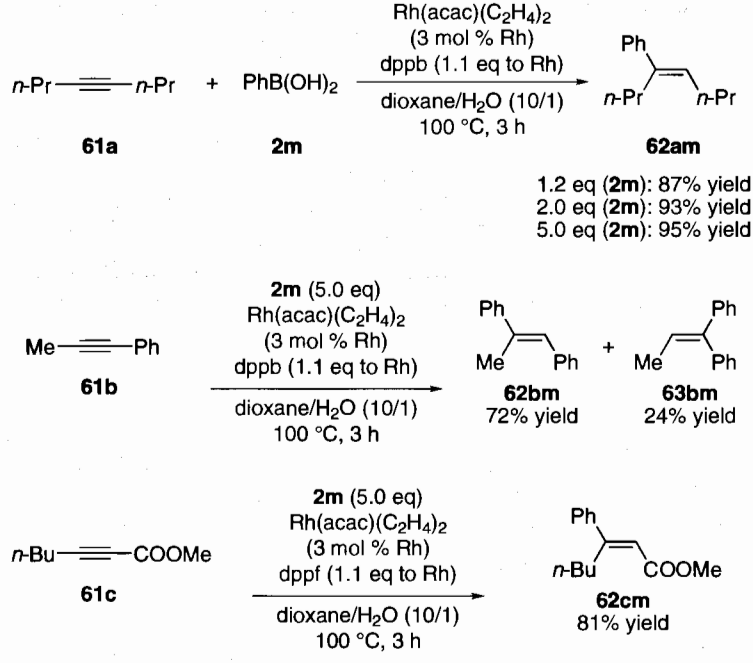
Krische and co-workers reported an intramolecular version of the tandem conjugate addition–aldol reaction. Enone-ketone **59** reacts with phenylboronic acid (**2m**) in dioxane containing 5 equiv. of water [40] (Scheme 4.26). This cyclization probably proceeds through the (oxa-π-allyl)rhodium intermediate. Because the intramolecular addition of the intermediate to the ketone is faster than protonolysis with water, the aldol product is obtained in high yields. Binap is a ligand of choice, leading to the conjugate addition–aldol product in up to 95% ee.



Scheme 4.26 Rhodium-catalyzed asymmetric intramolecular conjugate addition–aldol reaction.

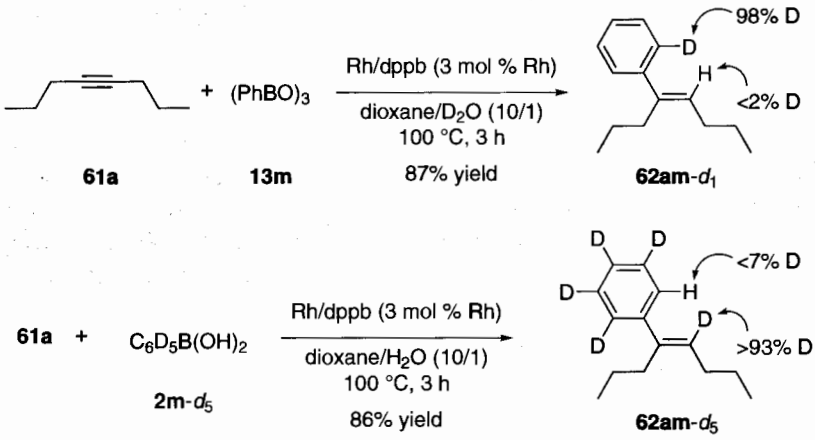
4.5
Addition of Organoboronic Acids to Alkynes

In 2001, the first rhodium-catalyzed hydroarylation of alkynes with arylboronic acids was reported by Hayashi [41]. For example, the reaction of 4-octyne (**61a**) with phenylboronic acid (**2m**) (1.2 equiv to **61a**) in the presence of 3 mol% of a rhodium catalyst generated from $Rh(acac)(C_2H_4)_2$ and dppb in dioxane–water (10:1) at 100 °C for 3 h gave a 87% yield of (*E*)-4-phenyl-4-octene (**62am**) (Scheme 4.27). An unsymmetrically substituted alkyne, 1-phenyl-1-propyne (**61b**), gave a mixture of (*E*)-1,2-diphenylpropene (**62bm**) and 1,1-diphenylpropene (**63bm**). Alkynes substituted with an electron-withdrawing group, such as methyl 2-heptynoate (**61c**), gave perfect regioselectivites, with the aryl group introduced selectively at the β position to the electron-withdrawing group.



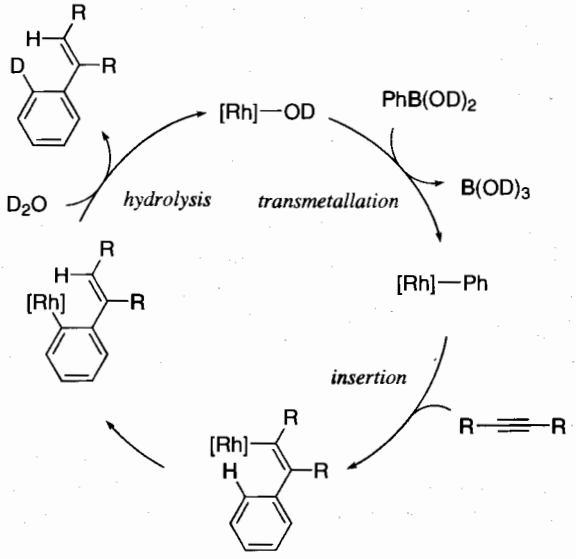
Scheme 4.27 Rhodium-catalyzed hydroarylation of alkynes with arylboronic acids.

To gain insight into the mechanism, deuterium labeling studies were carried out [41] (Scheme 4.28). 4-Octyne (**61a**) reacted with phenylboroxine (**13m**) in D_2O to give the unexpected hydrophenylation product **62am**-d_1, in which the deuterium was incorporated at the ortho position of the phenyl group and not at the vinylic position. Moreover, the reaction of **61a** with $C_6D_5B(OH)_2$ (**2m**-d_5) in H_2O gave the hydrophenylation product **62am**-d_5, where one of the deuterium atoms on the ortho position of the pentadeuteriophenyl moved to the vinylic position.



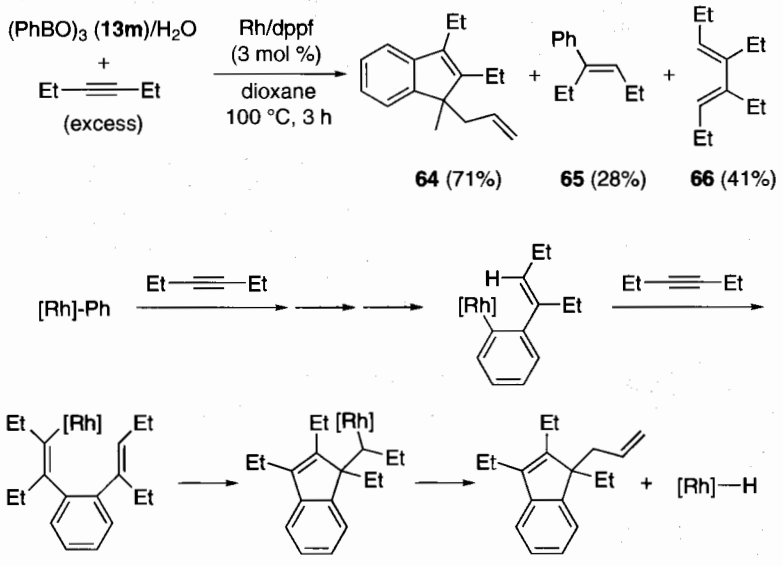
Scheme 4.28 Deuterium labeling studies for rhodium-catalyzed hydroarylation of alkynes with arylboronic acids.

The catalytic cycle was established by the outcome of these deuterium labeling studies. Thus, after transmetallation from boron to give the phenylrhodium species, the alkyne inserts into the phenyl–rhodium bond to form the alkenylrhodium intermediate (Scheme 4.29). It follows that rhodium moved from the vinylic position of the alkenylrhodium intermediate to the ortho position of the phenyl ring [42]. The so-formed 2-(alkenyl)phenylrhodium intermediate then undergoes hydrolysis with D_2O to give the deuterio phenylation product and the active hydroxorhodium intermediate.



Scheme 4.29 Catalytic cycle for the rhodium-catalyzed hydroarylation of alkynes with arylboronic acids.

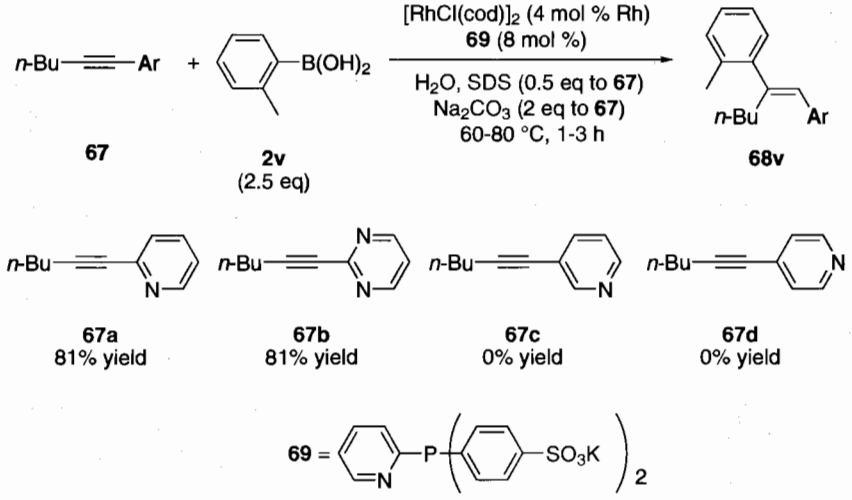
Based on this catalytic cycle, Hayashi foresaw that further insertion of an alkyne into the 2-(alkenyl)phenylrhodium intermediate could take place before the hydrolysis step. Indeed, this was accomplished by employing an excess of alkyne [41]. Thus, the reaction of phenylboroxine (**13m**) with 8 equivalent of 3-hexyne in the presence of one equivalent (to boron) of water and rhodium-dppf catalyst (3 mol%) in dioxane at 100 °C for 3 h gave a 71% yield of indene **64** together with the hydrophenylation product **65** (28%) and diene **66** (41%) (Scheme 4.30). The formation of indene **64** can be rationalized by a catalytic cycle involving addition of a 2-(alkenyl)phenylrhodium species to 3-hexyne and intramolecular carborhodation of the new alkenylrhodium intermediate. β-Hydrogen elimination on the resulting alkylrhodium species followed by isomerization of the double bond gives indene **64**, containing the allyl group, and a hydridorhodium species. The formation of diene **66** may suggest that the hydridorhodium comes back to the catalytic cycle after it effects the reductive dimerization of alkyne to form **66**. A similar formation of hydridorhodium species was also observed in the rhodium-catalyzed Heck-type reaction of arylboronic acids [32, 33] (Section 4.4).



Scheme 4.30 Rhodium-catalyzed tandem hydroarylation–carbocyclization of 3-hexyne with phenylboronic acid.

Lautens and Yoshida reported a similar rhodium-catalyzed hydroarylation of alkynes with arylboronic acids, where ortho nitrogen heteroaromatic alkynes were employed to favor a high regioselectivity [43]. The reaction of 2-(1-hexynyl)pyridine (**67a**) with 2-methylphenylboronic acid (**2v**) and $[RhCl(cod)]_2$/**69** catalyst in the presence of sodium carbonate and sodium dodecyl sulfate (SDS) in water gave a 84% yield of the addition product **68av** with high regioselectivity (Scheme 4.31). Under these conditions, the addition of arylboronic acids was also observed for several other or-

tho-alkynyl nitrogen heteroaromatic alkynes such as 2-alkynylpyrazole (**67b**), but no reaction was observed with either 3-alkynyl-(**67c**) or 4-alkynylpyridine (**67d**). In contrast to the deuterium labeling studies by Hayashi where a 1,4-shift was observed, deuterium was incorporated quantitatively at the alkenyl position when **67a** was reacted with **2v** in D_2O. These results are probably affected by the coordination ability of the nitrogen atom to the rhodium center.

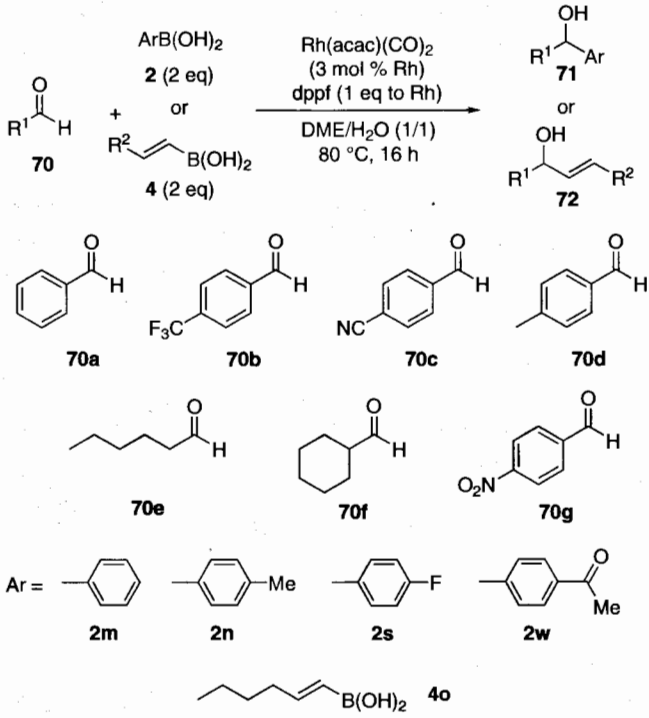


Scheme 4.31 Rhodium-catalyzed addition of arylboronic acids to alkynyl nitrogen heteroaromatic compounds.

4.6
Addition of Organoboronic Acids to Aldehydes and Imines

In 1998 Miyaura reported the first example of rhodium-catalyzed addition of organoboronic acids to aldehydes [44]. Optimal conditions were the use of 2 equivalents of boronic acid and a catalyst generated in situ from $[Rh(acac)(CO)_2]$/dppf complex in a 1:1 mixture of DME and water at 80 °C. Under these conditions, the addition of phenylboronic acid (**2m**) to benzaldehyde (**70a**) gave a 92% yield of diphenylmethanol (**71am**) (Scheme 4.32, entry 1) Reactions of phenylboronic acid (**2m**) with aldehydes **70b,c**, having an electron-withdrawing group on the phenyl ring, gave similar results (entries 2 and 3). However, addition to electron-rich aldehydes such as **70d–f** were slow (entries 4–6). Further, the reactions of arylboronic acids substituted with electron-donating groups such as *p*-tolylboronic acid (**2n**) gave high yields (entry 7), but the additions of electron-deficient arylboronic acids gave slow reactions under the same conditions (entries 8 and 9). Thus, the reaction is facilitated by the presence of an electron-withdrawing group on the aldehyde and an electron-donating group on the arylboronic acid. An exception was the reaction of 4-nitrobenzaldehyde (**70g**) with phenylboronic acid, which gave <1% yield of the product (entry 10). This result was

attributed to the coordination of the nitro group to the dppf complex, which would significantly retard the reaction. Addition of an alkenyl boronic acid, (*E*)-1-hexenylboronic acid (**4o**), was also successful (entry 11).



entry	aldehyde **70**	boronic acid **2** or **4**	alcohol **71** or **72**	yield (%)
1	**70a**	**2m**	**71am**	92
2	**70b**	**2m**	**71bm**	97
3	**70c**	**2m**	**71cm**	97
4	**70d**	**2m**	**71dm**	48 (76)[a]
5	**70e**	**2m**	**71em**	69
6	**70f**	**2m**	**71fm**	45 (95)[a]
7	**70c**	**2n**	**71cn**	99
8	**70c**	**2s**	**71cs**	52
9	**70c**	**2w**	**71cw**	<1
10	**70g**	**2m**	**71gm**	<1
11	**70c**	**4o**	**72co**	76

[a] The reactions were carried out at 95 °C for 16 h in dioxane/H_2O (1/1)

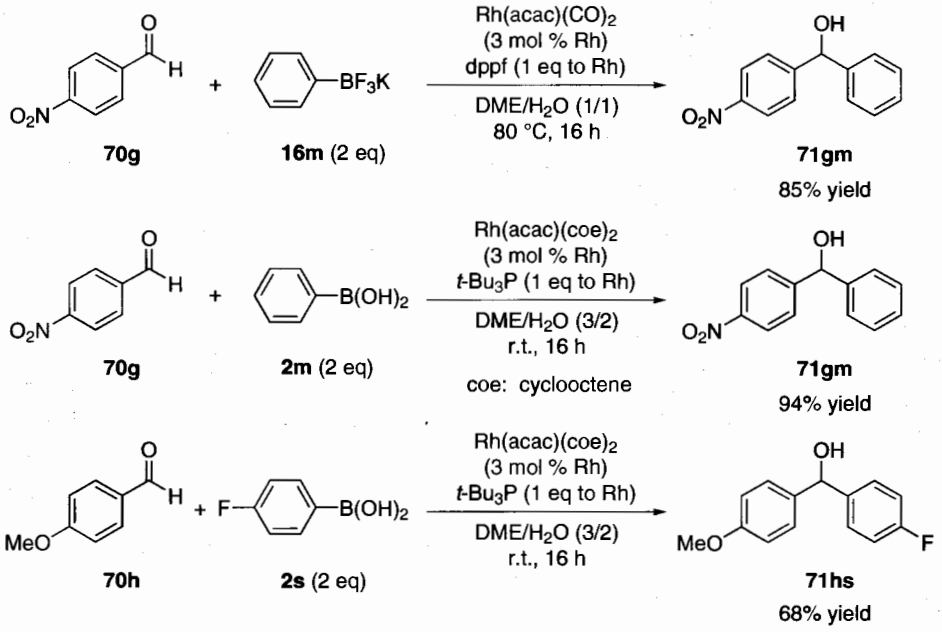
Scheme 4.32 Addition of organoboronic acids to aldehydes catalyzed by Rh(acac)$(CO)_2$/dppf.

After the initial report of Miyaura [44], several other modifications were reported (Scheme 4.33). Batey et al. employed potassium aryl- and alkenyltrifluoroborates in place of boronic acids [14a]. The relative rate of reaction was faster with organotrifluoroborates than with organoboronic acids. Phenyltrifluoroborate (**16m**) was successfully utilized with 4-nitrobenzaldehyde (**70g**), giving an 85% yield of **71gm**. A <1% yield of **71gm** was obtained when the corresponding boronic acid was used.

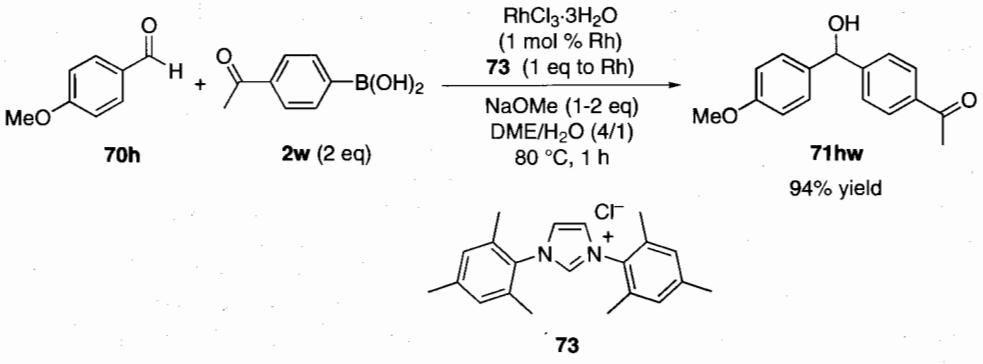
Ueda and Miyaura found that the bulky monodentate phosphine tri(*t*-butyl)phosphine is very effective for the rhodium-catalyzed addition of arylboronic acids to aldehydes [45] The reaction using 1 equiv of the phosphine to the rhodium metal proceeded even at room temperature. Phenylboronic acid (**2m**) reacted with 4-nitrobenzaldehyde (**70**g) to give 94% yield of **71gm**. 4-Methoxybenzaldehyde (**70h**), with a strong electron-donating group, and the electron-poor 4-fluorophenylboronic acid (**2s**) afforded the corresponding alcohol **71**hs.

Fürstner and Krause employed an *N*-heterocyclic carbene as a ligand [46], which have strong σ-donor and weak π-acceptor properties. Using a catalyst formed in situ from $RhCl_3 \cdot H_2O$ and imidazolium salt **73** in the presence of an aqueous base, the reaction of an aldehyde having an electron donating group (**70**h) and a boronic acid having an electron-withdrawing group (**2w**) was achieved in high yield.

Unfortunately, thus far there has been only one example of the asymmetric version of rhodium-catalyzed asymmetric arylation of aldehydes. In this report, by Miyaura [44], a rhodium complex coordinated with axially chiral monodentate phosphine ligand, (*S*)-MeO-mop, catalyzed the addition of phenylboronic acid (**2m**) to 1-naph-

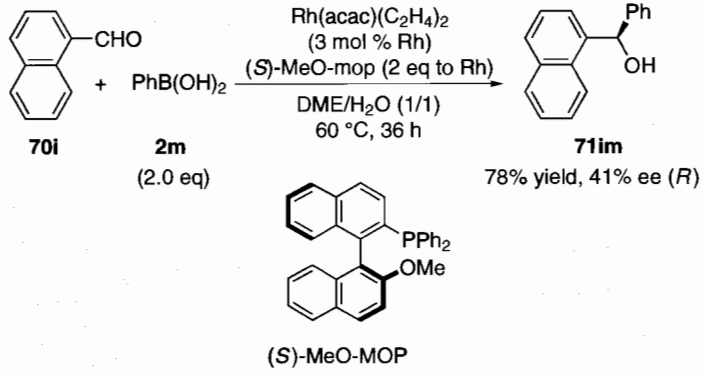


Scheme 4.33 Other conditions for the rhodium-catalyzed addition of organoboronic acids to aldehydes.



Scheme 4.33 Continued.

thoaldehyde (**70i**) in DME–H_2O at 60 °C for 36 h giving a 78% yield of diarylmethanol (*R*)-**71im** with 41% ee (Scheme 4.34). The use of chiral chelating bisphosphine ligands such as diop [44] and binap [44], and bisnitrogen ligands such as sparteine [47] and bisoxazoline [47] gave only racemic products.

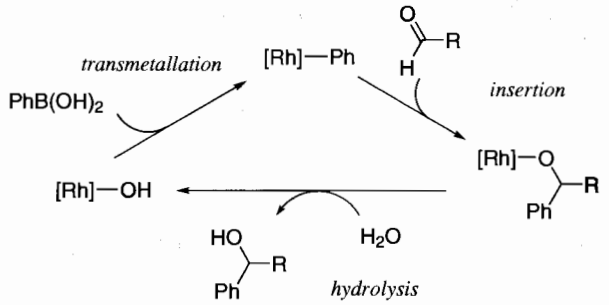


Scheme 4.34 Asymmetric rhodium-catalyzed addition of organoboronic acids to aldehydes.

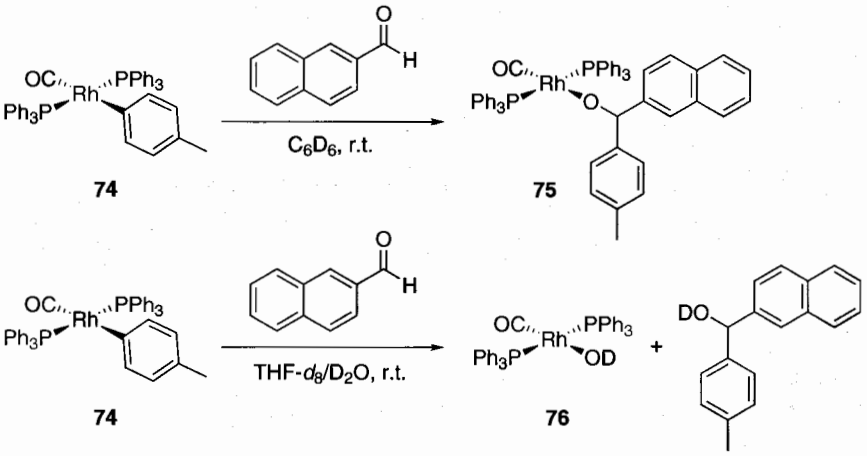
The proposed catalytic cycle [44] is very similar to that of 1,4-additions described in Scheme 4.4, consisting of steps (1) addition of phenylrhodium to aldehyde forming alkoxyrhodium species, (2) hydrolysis of the alkoxyrhodium giving the active hydroxorhodium species, and (3) transmetallation of a phenyl group from boron to the hydroxorhodium regenerating the phenylrhodium intermediate (Scheme 4.35).

In 2002, Kurg and Hartwig observed directly aldehyde insertion into an arylrhodium species [48]. Arylrhodium complexes are mostly unstable to isolate, but a rhodium analogue of Vaska's complex **74** was easier to handle. The reaction of **74** with 2-naphthaldehyde in benzene-d_6 at room temperature gave alkoxyrhodium intermediate **75**, which was observed directly by ^1H and ^{31}P NMR spectroscopy (Scheme 4.36). On treatment of **74** with 2-naphthaldehyde in a mixture of THF-d_6 and D_2O, hy-

droxorhodium **76** and diarylmethanol were formed. These results support the mechanism proposed in Scheme 4.35.



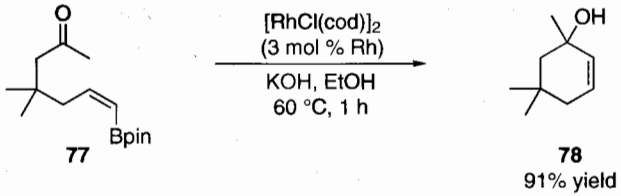
Scheme 4.35 Catalytic cycle for rhodium-catalyzed addition of organoboronic acids to aldehydes.



Scheme 4.36 Control reactions of arylrhodium complex **74** with 2-naphthaldehyde.

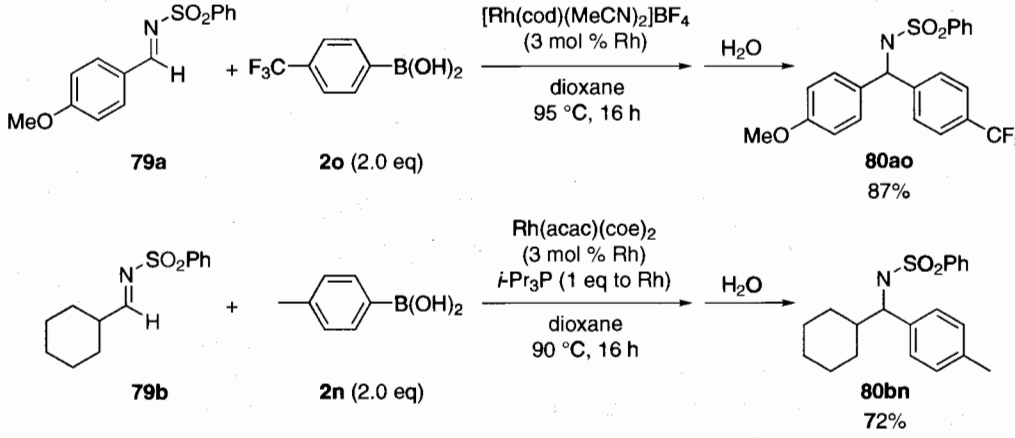
There has been only one example of a rhodium-catalyzed addition of organoboronic reagents to ketones so far. Miyaura and co-workers reported an intramolecular cyclization of pinacol ester **77** using $[RhCl(cod)]_2$ catalyst in the presence of potassium hydroxide, affording cyclic alcohol **78** in high yield [49] (Scheme 4.37).

Miyaura also [50] reported rhodium-catalyzed additions of arylboronic acids to aldimines. Despite the potential production of water from boronic acids by cyclic trimerization, no hydrolysis of *N*-sulfonyl aldimines was observed when boronic acids were used in the rhodium-catalyzed addition to aldimines in anhydrous dioxane. The reactions proceeded well, regardless of the presence of both an electron-withdrawing and an electron-donating group on the aldehyde or the arylboronic acid. For example, the reaction of *N*-sulfonyl aldimine **79a** with boronic acid **2o** catalyzed by cationic rhodium $[Rh(cod)(MeCN)_2]BF_4$ gave 87% yield of the product **80ao**, and



Scheme 4.37 Rhodium-catalyzed intramolecular addition of organoboronates to ketones.

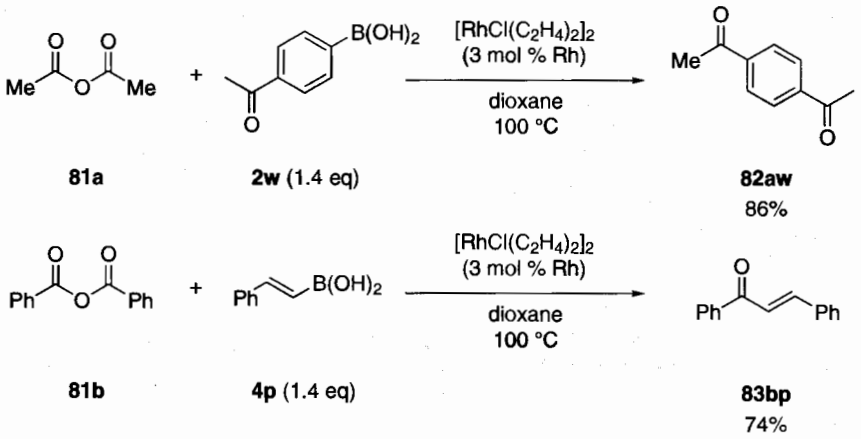
alkyl aldimine **79b** reacted with boronic acid **2n**, catalyzed by a complex generated from [Rh(acac)(coe)2] and *i*-Pr3P, to give **80bn** (72% yield) (Scheme 4.38).



Scheme 4.38 Rhodium-catalyzed addition of organoboronic acids to N-sulfonyl aldimines.

4.7
Addition of Organoboronic Acids to Anhydrides

Frost and Wadsworth reported that organoboronic acids react with anhydrides to give ketones [51] (Scheme 4.39). The addition of **2w** to acetic anhydride (**81a**) in the presence of [RhCl(C_2H_4)2]2 in dioxane gave a 86% yield of the corresponding ketone **82aw**. Under these conditions, a high yield of product was also obtained in the addition of alkenylboronic acid **4p** to benzoic anhydride (**81b**), giving a 74% yield of **83bp**. Similar results using tetraphenylborate have been reported by Nomura and co-workers [52].



Scheme 4.39 Rhodium-catalyzed addition of organoboronic acids to anhydrides.

4.8 Outlook

Rhodium-catalyzed addition of organoboronic acids to electron-deficient olefins and carbonyl compounds has emerged as a new useful method for organic synthesis. Such carbon–carbon bond formation is one of the most efficient reactions in terms of both chemoselectivity and enantioselectivity. Organoboronic acids have marked advantages over organomagnesium and -lithium reagents in their stability in air and ease of handling. The addition reactions have been extended to other organometallic reagents such as tin (Sn) [53], silicon (Si) [54], titanium (Ti) [55], bismuth (Bi) [56], and zirconium (Zr) [57], and some reactions using these reagents have important advantages over those that employ organoboron reagents. Recent reports on the use of palladium-catalyst systems for the addition of organoboron reagents are remarkable, with higher reactivity than that of the rhodium catalysts observed in some cases [58].

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5
Recent Advances in Copper-promoted C–Heteroatom Bond Cross-coupling Reactions with Boronic Acids and Derivatives

Dominic M. T. Chan and Patrick Y. S. Lam

5.1
General Introduction

The Pd-catalyzed Suzuki–Miyaura coupling is perhaps one of the most powerful and effective methods for carbon–carbon (C–C) bond formations developed in recent years. In particular, Suzuki–Miyaura cross-coupling is now the method of choice for the construction of biaryl compounds. The ready commercial availability of a diverse set of aryl boronic acids [1] and myriad of literature citations [2] testify to the robustness of this methodology. The corresponding aryl carbon–heteroatom (C–X, where X = O, N, S) bond cross-coupling, however, is less well established. This transformation is equally desirable because aryl ethers, anilines, and aryl thioethers are ubiquitous moieties in a wide range of molecules with many important applications, especially in the areas of pharmaceutical and crop protection research. Chemistry to generate aryl amines and aryl ethers does exist in the literature; e.g. the classical copper-mediated Ullmann reaction, and palladium-catalyzed C(aryl)–N bond formation with aryl halides developed by Buchwald and Hartwig [3]. However, many of these methodologies involve harsh conditions, such as high temperatures and/or strong bases, or the use of very expensive Pd catalysts.

The recent development of copper(II)-promoted O- and N-arylation with boronic acids is a major breakthrough in this respect (Equation 1 illustrates a prototype). One reason for its gaining in popularity is the mild reaction conditions needed, e.g. room temperature, weak base, and ambient atmosphere. This approach also takes advantage of the ready availability of the boronic acids and the chemistry developed in the Suzuki coupling arena.

Since its discovery, the authors of this chapter and other research groups have made considerable progress in expanding this copper-mediated cross-coupling methodology and large body of literature has appeared concerning the scope and mechanism of this reaction. In addition, different aspects of this chemistry have been surveyed by several authors [2b, 3, 4]. The recent review by Thomas and Ley published in late 2003 is perhaps one of the best-written and most comprehensive [3].

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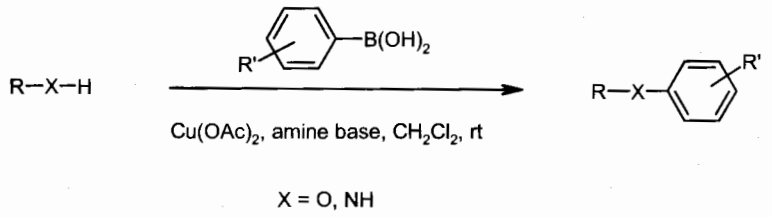


(1)

This review will focus primarily on recent work *not* covered by Thomas and Ley, as well as a significant quantity of unpublished work from our laboratories. An account of Chan's original discovery, and Chan and Lam's initial studies will first be presented. The main body of this chapter will involve examination of various types of C–X cross-coupling using boronic acids and their derivatives, as well as mechanistic considerations. Readers are encouraged to peruse the aforementioned reviews for a more complete survey of the earlier development of this area.

5.2
Copper-mediated Boronic Acid C–O and C–N Cross-coupling – Historical Background

The journey begins in early 1994 in the laboratory of Chan at the DuPont Crop Protection Department with the quest for a mild and efficient way to arylate N–H and O–H bonds. Early success was obtained in the improvement of Barton's bismuth arylation chemistry, where it was discovered that addition of an amine promoter (e.g. triethylamine or pyridine) greatly enhances the scope and yields of the reactions [5]. The popularity of the Suzuki coupling at that time prompted Chan to study the replacement of the triarylbismuth reagents with the corresponding arylboronic acids. Consequently, novel C–O and C–N boronic acid cross-coupling methodology was demonstrated successfully in Chan's laboratory by the end of 1994. In collaboration with M. Winters, a colleague at that time, Chan further explored the area. Their preliminary results were communicated through DuPont internal circulation to Lam, who was then with DuPont Merck Pharmaceuticals and was exploring various methods for N-arylation. Lam further explored the chemistry and greatly expanded the scope of the reaction, including the use of alkenylboronic acids, siloxanes, and stannanes. Concurrently, his group demonstrated the generality of the N-arylation with many heterocyclic systems, as well as developing catalytic processes.

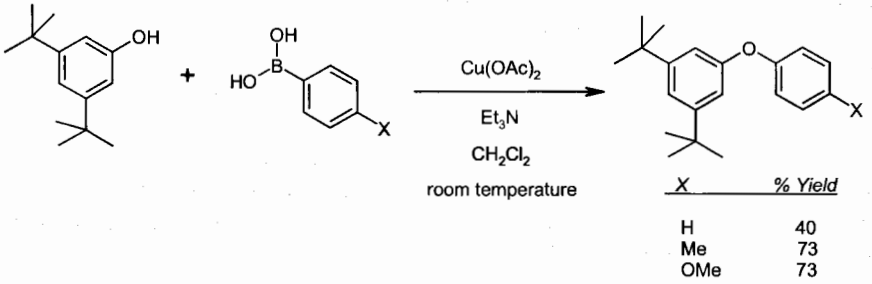
In June 1997, Chan presented the early results of his work as part of a poster at the 35th National Organic Symposium in San Antonio, TX [6]. One of Prof. D. Evans' group members present during that meeting took this chemistry back to Harvard University. The boronic acid arylation methodology was then further optimized by Evans and co-workers with the sole emphasis on application to biaryl ether synthesis. The cumulated research effort in these three laboratories was finally disclosed in three back-to-back publications in 1998 [7–9]. Since then, the area has continued to attract attention and further refinement, as evidenced by the increasing number of research groups around the world adopting this methodology and publishing their re-

sults. This is perhaps a testimony to the ease, versatility, and robustness of this methodology. Recent developments include further expansion of the scope of the substrates and the boron reagents, fine tuning of the reaction with various solvents and additives, as well as the development of new solution- and solid-phase catalytic systems.

5.3
C(aryl)–O Cross-coupling

5.3.1
Intermolecular C–O Cross-coupling

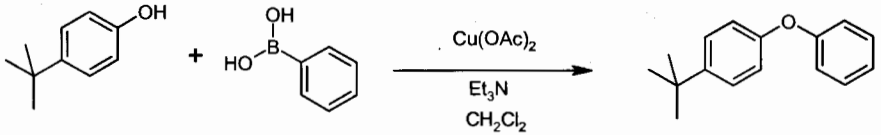
The original protocol of Chan and co-workers for phenol arylation involves simply stirring the phenol with an aryl boronic acid (2–3 equiv.), anhydrous copper(II) acetate (1–2 equiv.), and Et_3N (2–3 equiv.) in methylene chloride at room temperature for 1–2 days. Workup entails removal of the volatiles in vacuo followed by direct column chromatography of the crude material to obtain the biaryl ether product. Yields are reasonable, with electron-rich aryl boronic acids performing better than the unsubstituted parent boronic acid, as exemplified in the arylation of 3,5-di(*t*-butyl)phenol (Scheme 5.1) [7].



Scheme 5.1 Arylation of 3,5-di(*t*-butyl)phenol with arylboronic acids.

Evans' study further expands the scope of this reaction and demonstrates its synthetic utility in an expedient synthesis of thyroxine [8]. With the parent phenylboronic acid and 4-*t*-butylphenol as the model substrates, the use of up to 5 equiv. of base could further improve the reaction (Scheme 5.2). Of the other Cu(II) sources examined, $Cu(OPiv)_2$, $Cu(NO_3)_2$, $Cu(acac)_2$, and $Cu(TFA)_2$ also promoted the arylation, but with yields inferior to those obtained with $Cu(OAc)_2$. Other salts like $CuSO_4$, $CuCl_2$, $Cu(ClO_4)_2$, and $Cu(OTf)_2$ all failed. Performing the reaction under *oxygen* or an *ambient atmosphere* is also advantageous. In one case where only 10 mol% of $Cu(OAc)_2$ was used, the reaction gave a 30% yield under oxygen versus only 9% if the reaction was performed under argon. This observation sets the stage for the development of catalytic processes, which will be discussed below. Evans and co-workers also discovered that adding powdered 4Å molecular sieves can serve to suppress the formation

of phenol and diphenyl ether. They postulated that these side-products derived from the competitive arylation of water, which was generated in the cyclodehydration of phenylboronic acid to the triphenylboroxine under the reaction conditions (vide infra). Notably, the groups of Chan and Tokunaga have independently observed the spontaneous conversion of phenylboronic acid into the boroxine in CH_2Cl_2 at room temperature [10]. Evans and co-workers also reported that the phenylboronic acid could be replaced by 0.33 equiv. of triphenylboroxine to furnish similar yields of desired products.



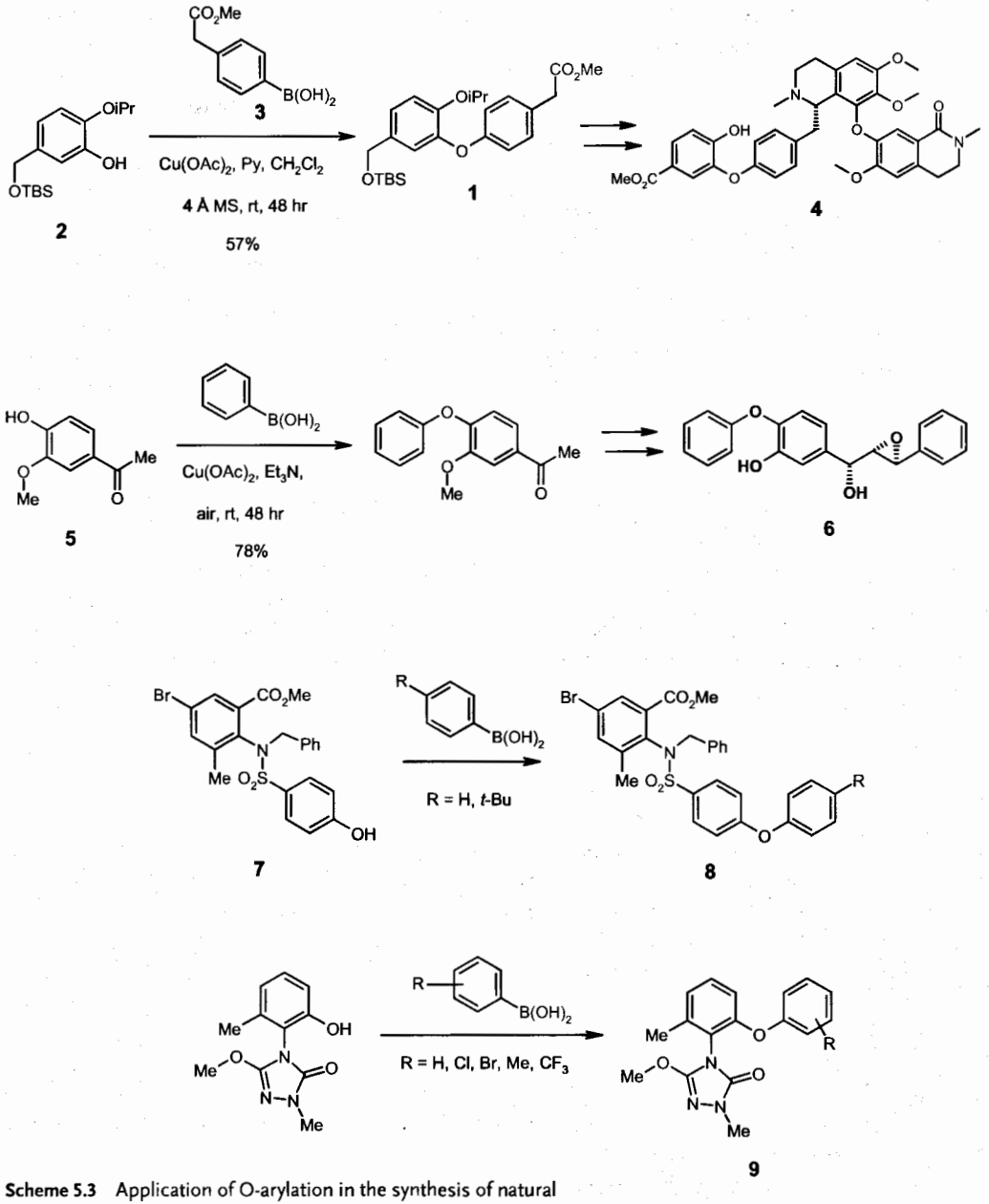
equiv. $Cu(OAc)_2$	atmosphere	equiv. base	% Yield
1.0	Argon	0	10
1.0	Argon	2	26
1.0	Argon	4	33
1.0	Argon	10	34
0.1	Argon	5	9
0.1	Oxygen	5	30
1.0	Ambient	1	41
1.0	Ambient	5	71
1.0	Ambient	10	71
1.0	Oxygen	5	71

Scheme 5.2 Arylation of 4-*t*-butylphenol with phenylboronic acid.

Recently, many groups have utilized the boronic acid arylation strategy in the synthesis of many biologically important molecules. The protocol developed by Evans remains the method of choice for many of these applications.

For example, the aryl ether **1**, obtained from the coupling of phenol **2** with boronic acid **3**, serves as a starting point for the first enantioselective total synthesis of (–)-tejedine (**4**) [11]. Phenylation of phenol **5** provides the requisite starting material for a preparation of the novel epoxychalcanol **6**, which was used in a structural investigation of the natural product puetuberosanol [12]. Biaryl ethers of the general structure **8**, which are anthranilic acid–base inhibitors of matrix metalloproteinase, were prepared from phenol **7** via cross-coupling with phenyl- and 4-*t*-butylphenylboronic acids [13]. Chan and co-workers have also applied the O-arylation methodology in the synthesis of fungicidal active biaryl ethers (**9**) containing a triazolinone moiety [14] (Scheme 5.3).

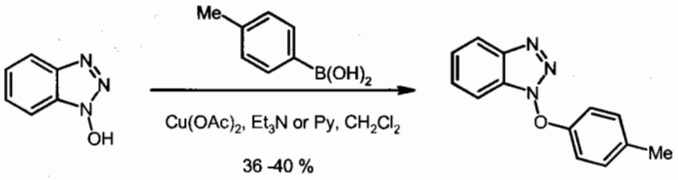
Kelly and co-workers have shown that *N*-hydroxyphthalimide undergoes copper-mediated cross-coupling with a diverse set of arylboronic acids to give the corresponding O-arylated products in reasonable yields. Pyridine turned out to be the best amine base for this reaction – better than Et_3N, 4-dimethylaminopyridine (DMAP), Cs_2CO_3, and DABCO. Interestingly, of all the copper salts screened, Cu(I)Cl and



Scheme 5.3 Application of O-arylation in the synthesis of natural product and bioactive compounds.

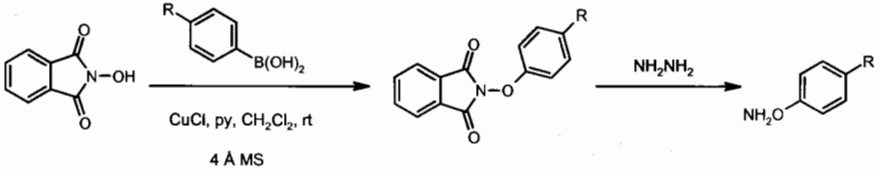
$Cu(I)Br \cdot SMe_2$ perform equally as well as $Cu(OAc)_2$. Removal of the phthalimidyl moiety of the O-arylated products with hydrazine hydrate has been demonstrated in a few cases. Thus, this approach represents a novel route to O-aryloxyamines from commercially available starting materials [15] (Scheme 5.4). Similarly, Lam and co-

workers were able to arylate *N*-hydroxybenzotriazole to provide the corresponding O-phenylated product [16] (Equation 2).

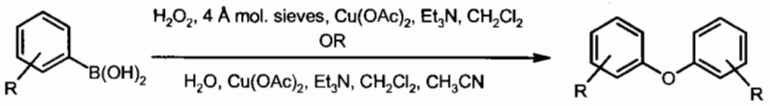


(2)

There are two reports of the application of this chemistry to the preparation of symmetrical biaryl ethers. One approach by Prakash and co-workers involves an in situ oxidation of the boronic acid with H_2O_2 (0.25 equiv.), followed by addition of 4Å molecular sieves, $Cu(OAc)_2$ (0.5 equiv.) and Et_3N (0.5 equiv.) [17]. The protocol developed by Sagar et al. entails simply stirring the boronic acid (1 equiv.), $Cu(OAc)_2$ (1 equiv.), Et_3N (5 equiv.), and water (10 equiv.) in methylene chloride and acetonitrile [18] (Equation 3). However, notably, biaryl ether formation is a typical side reaction in O- and N-arylations.



Scheme 5.4 Application of O-arylation in aryloxyamine syntheses.



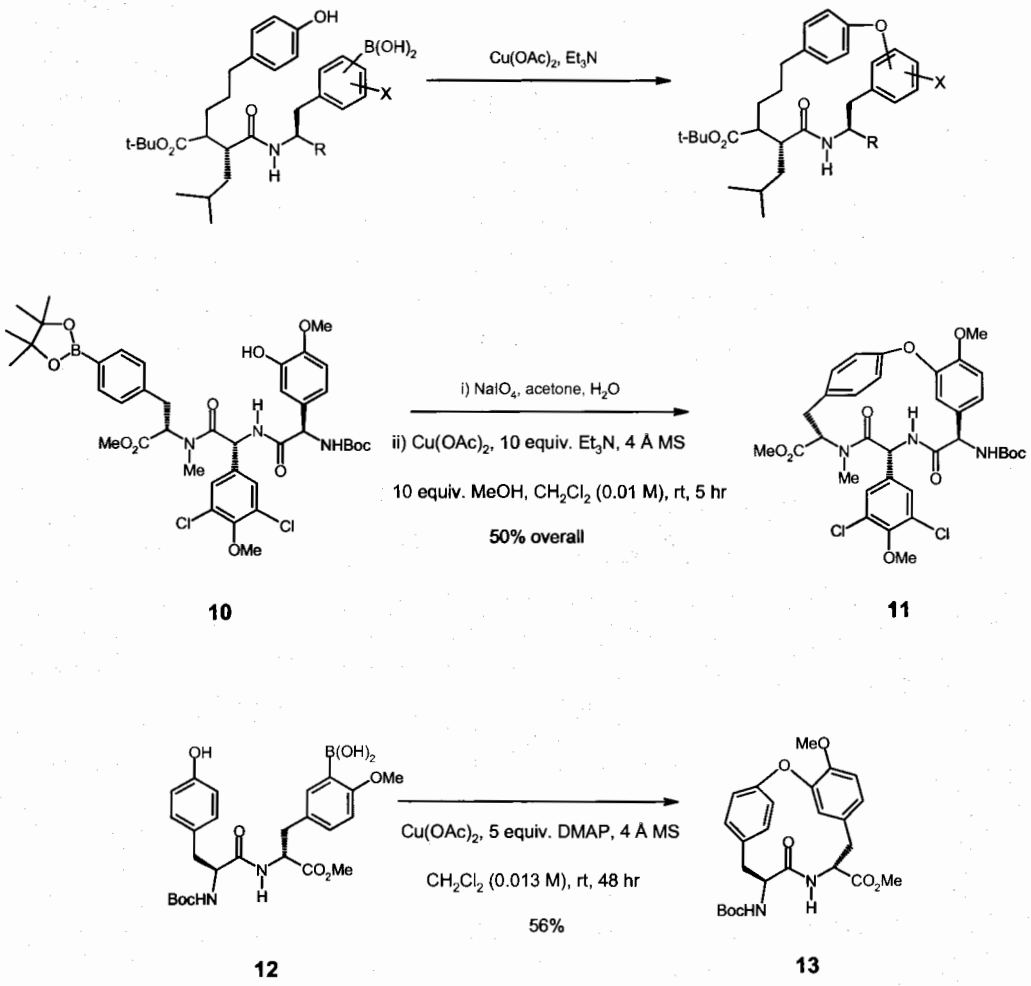
(3)

5.3.2
Intramolecular C–O Cross-coupling

Since the early success of Decicco et al. [19] in extending the boronic acid cross-coupling to an intramolecular system, more examples of this approach have appeared in the literature (Scheme 5.5). Snapper and Hoveyda reported a total synthesis of the anti-HIV natural product chloropeptin 1 in which the crucial biaryl ether moiety was constructed via the Cu-mediated reaction (Scheme 5.5) [20]. Thus, treatment of the boronic ester **10** with $NaIO_4$ liberates the boronic acid, which then cyclizes under $Cu(OAc)_2$ to give the biaryl ether **11**, a precursor to the final target. In this case, the addition of **10** equiv. of methanol was critical for efficient intramolecular cross-coupling. The authors proposed that the excess methanol increases the solubility of the

Cu salt and/or generates a dimethyl boronic ester. The latter explanation is consistent with Chan's observation with boronic acid esters (vide infra) [10].

Takeya et al. reported another application in the synthesis of cycloisodityrosines (Scheme 5.5) [21]. For the cyclization of **12** into **13**, the use of DMAP as the amine base gives better results than using either Et_3N or pyridine, with no epimerization at any of the stereogenic centers. Besides providing a higher yield, DMAP also appears to suppress the protodeboronation of **12**. In contrast, an earlier paper by Boger and co-workers reported only a 9% yield in the cyclization of a very similar substrate using essentially the original Chan protocol [22].

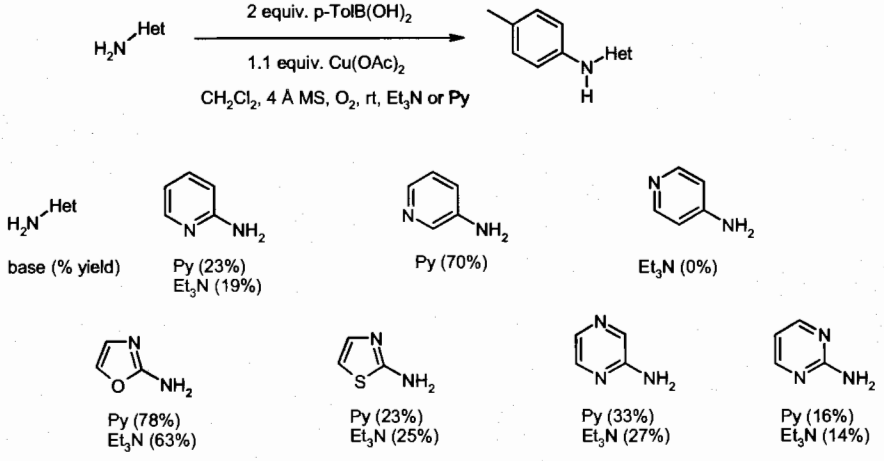


Scheme 5.5 Examples of intramolecular C–O cross-coupling.

5.4
C–N Cross-coupling

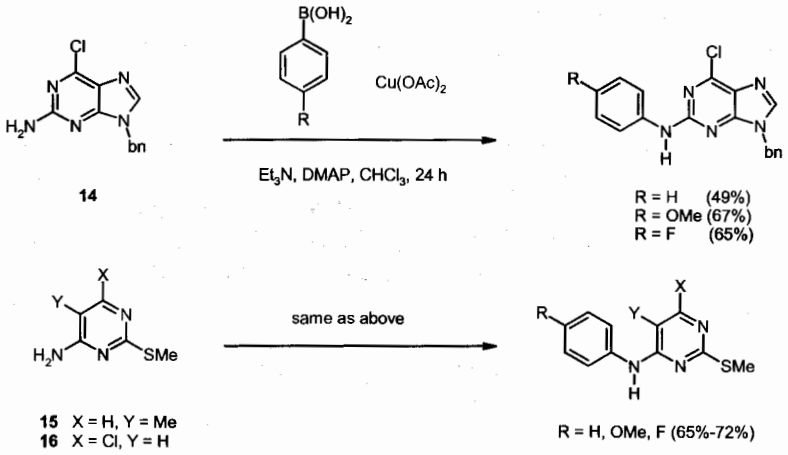
5.4.1
C–N (Non-heteroarene NH) Cross-coupling

As mentioned above, a clear advantage of this methodology is the broad scope of substrates that successfully participate in the arylation. The initial studies by Chan demonstrate a wide range of NH-containing substrates that will undergo N-arylation [7]. These include amines, anilines, amides, imides, ureas, carbamates, and sulfonamides. In general, substrates with nucleophilic- or electron-rich nitrogen tend to give better reactions, although the presence of other chelating nitrogen in the molecule can sometimes influence the chemistry. For example, while 3-aminopyridine gives a 70% yield of arylated product with *p*-tolylboronic acid and pyridine as the promoter, 2-aminopyridine proceeds with lower yield and 4-aminopyridine fails completely. Other amino heterocycles also produce variable results (Scheme 5.6) [23a, b]. Cross-coupling of aminopurines **14** and aminopyrimidines **15** and **16** with arylboronic acids gave N-arylated products in moderate to good yields (Scheme 5.7) [24]. N-Aminoazoles **17–20** have been reported to undergo phenylation with phenylboronic acid (2 equiv.) under typical conditions (Scheme 5.8) [25].

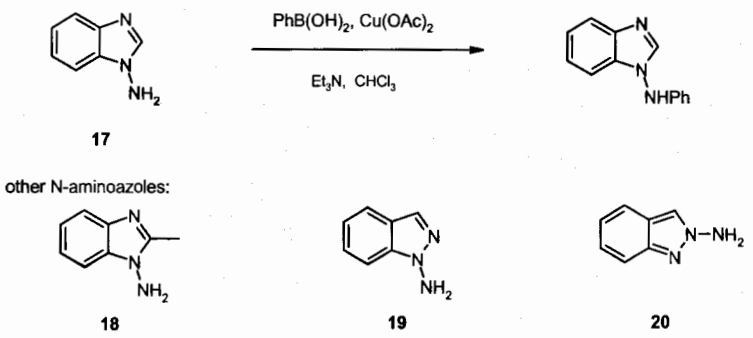


Scheme 5.6 C–N cross-coupling of heterocyclic amines.

In a significant recent advancement of this methodology, Xie and co-workers showed that the reaction can be carried out in the presence of a catalytic amount of a copper salt such as $Cu(OAc)_2$ hydrate or CuCl, in refluxing methanol in a much shorter time of only 10 min to 3 h (Scheme 5.9) [26]. The use of methanol as the solvent is consistent with the reported advantage of added methanol in the intramolecular C–O cross-coupling discussed earlier. It is not too surprising that the reactions proceed faster at higher temperature, but, notably, no amine base is used in this study, an observation that has only been reported twice in recent literature. The first

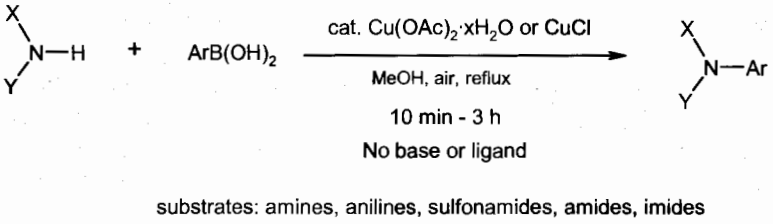


Scheme 5.7 C–N cross-coupling of aminopurines and aminopyrimidines.

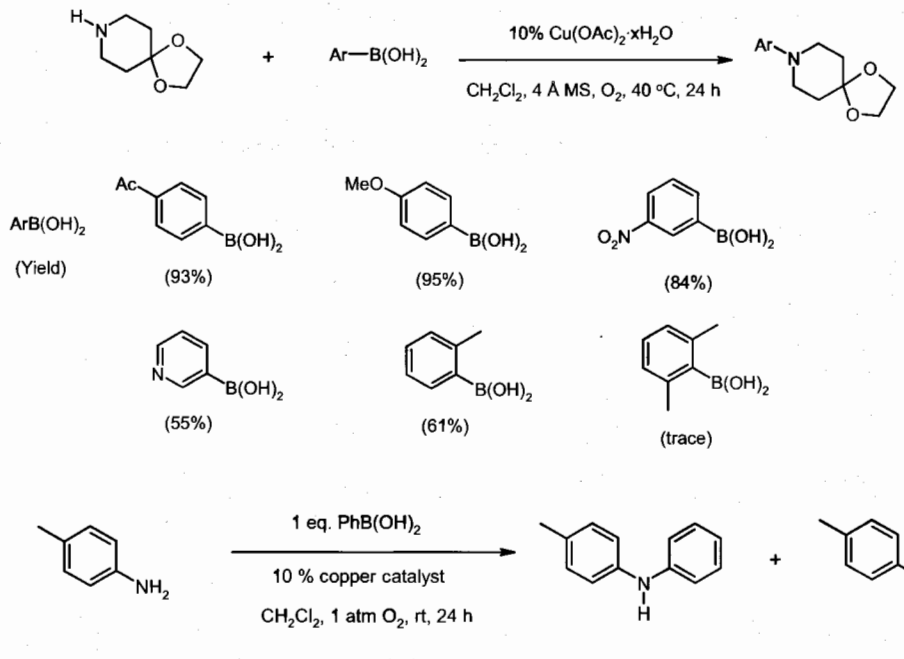


Scheme 5.8 C–N cross-coupling of N-aminoazoles.

report is by Quach and Batey in a catalytic system with butyl amine, *p*-bromoaniline, or a piperidine substrate in methylene chloride (Scheme 5.10) [27]. The other is by Corain and co-workers in a study of the reaction of *p*-toluidine with phenylboronic acid (Scheme 5.10) [28a]. Here, the authors obtained higher conversions of toluidine without the base, and thus speculated that Et_3N can inhibit the reaction. However, in the absence of Et_3N, selectivity for the arylated product is lower, mainly due to the formation of boronic acid monoamide adduct **21**. Interestingly, **21** is not formed in the absence of a copper catalyst. Thus, one possible role of the tertiary amine base is to coordinate with the boronic acid to suppress the formation of this amide adduct.



Scheme 5.9 Catalytic C–N cross-coupling in methanol.



Catalyst	*%Conversion*	*% Yield*
$Cu(OAc)_2$ + 2 equiv. Et_3N	41	37
$Cu(OAc)_2$ (no base)	77	43
MPI-Cu + 2 equiv. Et_3N	34	21
MPI-Cu (no base)	65	53

Scheme 5.10 Base/ligand free catalytic C–N cross-coupling.

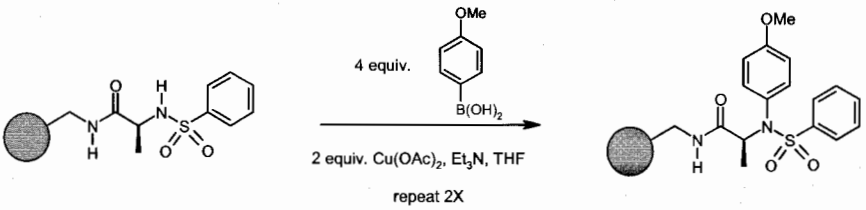
5.4.1.1 Application in Solid-phase Synthesis

One of the most exciting applications of this copper-mediated reaction is in solid-phase synthesis and combinatorial chemistry. Two approaches have been reported: solid-supported catalyst and resin-supported substrates.

Corain and co-workers have developed a novel methacrylic resin supported copper catalyst (MPI-Cu) with a catalytic performance comparable to that of $Cu(OAc)_2$ (Scheme 5.10) [28a]. Recently, another solid-phase copper catalytic system with a beta-ketoester linkage has been reported by Chiang and Olsson for N- and O-arylation, although the turnover is lower in this case [28b]. Obviously, the supported catalyst will have the added advantage of easy recovery and recycling.

Combs and co-workers have pioneered the effort in the use of resin-supported substrates, reporting many examples of efficient cross-coupling of solid-supported sulfonamides [28c], primary and secondary aliphatic amines [28d], as well as heteroarenes such as benzimidazoles, imidazoles, pyrazoles, and benzotriazoles [28e].

In the heteroarene case, reactions could be driven to completion with the aid of microwave irradiation. Scheme 5.11 gives an example of the resin-bound sulfonamide arylation [28c]. Combs' work has been extensively reviewed by Thomas and Ley [3].



Scheme 5.11 Catalytic C–N cross-coupling on solid support.

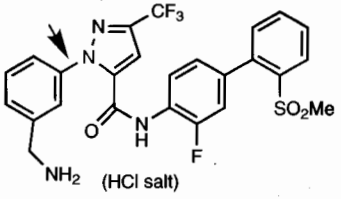
5.4.2
C–N (Heteroarene) Cross-coupling

Lam and co-workers, while working on the design and discovery of pyrazole Factor Xa inhibitors (e.g. Pinto's DPC 423 [29a] in Scheme 5.12) as novel anticoagulants, required mild reaction conditions for the N-arylation of azoles [29b]. No mild method to generate heteroarene-arene C–N bonds existed at the time. The state-of-the-art chemistry was Buchwald–Hartwig's palladium N-arylation chemistry with aryl halides. However, this reaction does not work for N-arylation of azoles like imidazoles and pyrazoles. A search of a natural products database revealed that this type of C–N bond does not exist in non-protein natural products (Scheme 5.13). As a result, the methodology to generate this bond has been largely under-explored over the years by academic groups since natural products have always been the prominent targets. In addition, in material science, polyanilines and polythiophenes have been extensively explored for their properties as organic conductors. However, because of the lack of mild methods to make polyheteroarenes, very few novel ones are known. For example, C–N linked polybenzimidazoles, polyindazoles and polybenztriazoles are in theory mimics of polyanilines. The synthesis and study of these novel polyheteroarenes should be a fertile ground for material science research if a mild method of N-arylation is available. With these two objectives in mind the search for mild methods of N-arylation of heteroarenes was initiated (Scheme 5.14).

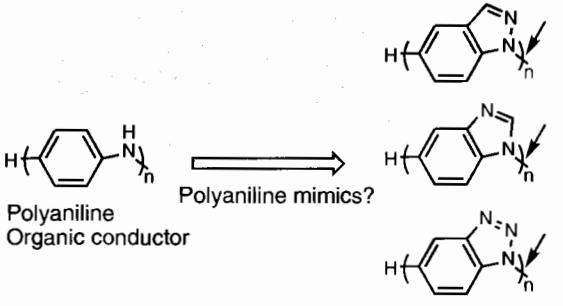
Lam discovered that imidazoles and pyrazoles underwent N-arylation with 2.0 equiv. of *p*-tolylboronic acid under typical conditions (Scheme 5.15) [9]. Electron-poor azoles such as triazoles and tetrazole gave poor yields. Recently, Clark and co-workers [30] reported N-arylation at the N-2 position of 4,5-diaryl-1,2,3-triazole (no specified yield) (Scheme 5.15). This is in contrast to the results on the parent 1,2,3-triazole where N-arylation occurs on N-1 [9]. The regiochemical preference of Clark's system can be explained by the high sensitivity to steric hindrance of these cross-coupling reactions (vide infra).

The parent pyrroles and indoles gave very poor yields (see Appendix, Section 5.12). However, Mederski [31], and Srirangam and co-workers [32] showed that N-arylation

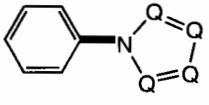
proceeded in good yields when there is a chelating aldehyde, ketone or ester alpha to the NH group. In contrast, for phenylalanine, which has an α-carboxylate group, no N-arylation was observed indicating that the α-carboxylate has a deleterious effect, probably due to tight binding to the copper center [23a, b].



DPC 423 clinical candidate
BMS novel Factor Xa inhibitor as anticoagulant
FXa K_i = 0.15 nM

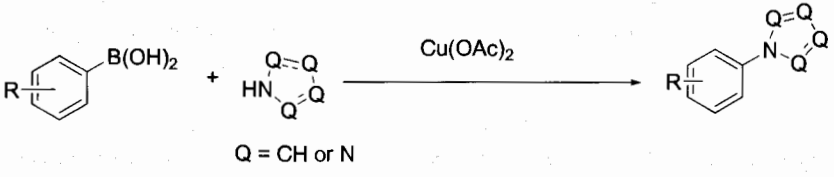


Scheme 5.12 Novel compounds containing heteroarene–arene C–N bonds.



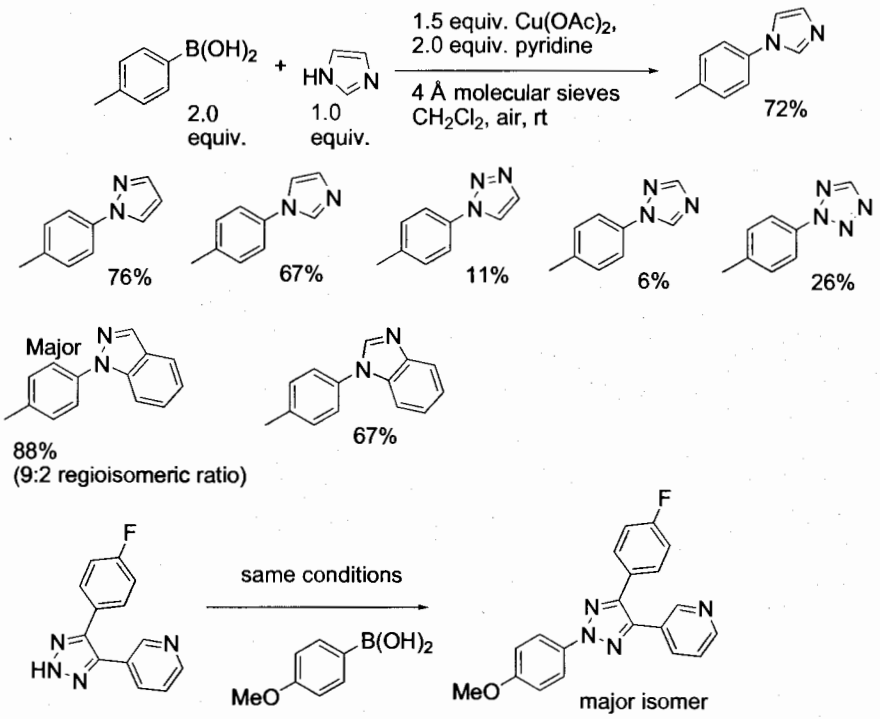
Substructure search of natural products database yielded 0 hit.

Scheme 5.13 Substructure search of natural products database.



Scheme 5.14 Copper-promoted N-arylation of heteroarenes.

Xie and co-workers reported the N-arylation of imidazole in *refluxing methanol* in the presence of catalytic cuprous chloride or cupric acetate in air [26]. Yields are higher than the catalytic $[Cu(OH)\cdot TMEDA]_2Cl_2$ condition first introduced by Collman and co-workers [33a, b]. Similarly, the same conditions are applicable to phthalamides [26], also with better yields than previously reported by Lam and co-workers [33c]. Conversely, for aniline and sulfonamide substrates, Xie's conditions gave lower yield than Lam's conditions [33c]. Likewise, for basic amines, Batey's conditions [27] are superior.

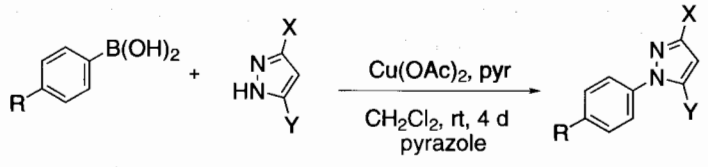


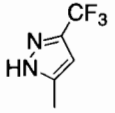
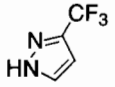
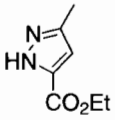
Scheme 5.15 N-Arylation of azoles.

5.4.2.1 Factor Xa Inhibitors

In Lam and co-workers' research on the N-arylation of pyrazoles as Factor Xa inhibitors [29], the regioselectivity was studied (Scheme 5.16) [34]. For the first two pyrazoles, N-arylation occurred at the less hindered nitrogen. For the third pyrazole, 30% of the minor regioisomer was obtained. In this case, the α-activating ester is the directing group even though it is bigger than the methyl group. In general, for many substrates besides pyrazoles, the reaction is very sensitive to steric effects.

Subsequently, N-arylated pyrazoles can undergo deprotonation by *n*-butyllithium and reaction with phenylisocyanate to generate moderately substituted pyrazoles as Factor Xa inhibitors. The aniline portion of the Factor Xa inhibitor can also be formed by using aryltrimethoxysiloxane as organometalloid (Scheme 5.17) [35].

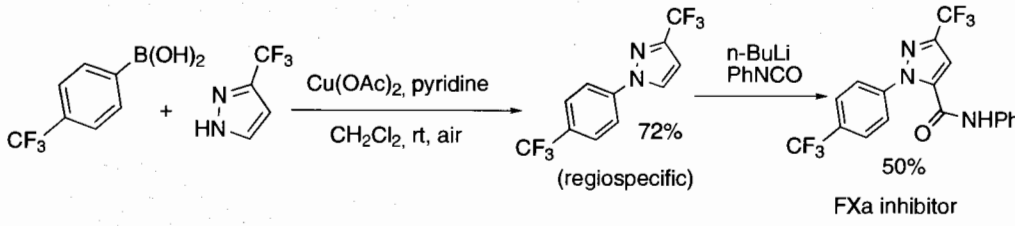


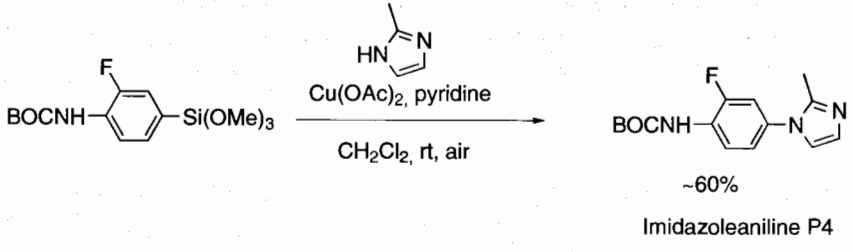
pyrazole	R	X	Y	% yield
	CF_3	CF_3	CH_3	70
	CH_3	CF_3	CH_3	70
	OMe	CF_3	CH_3	58
	CF_3	CF_3	H	72
	CH_3	CF_3	H	70
	OMe	CF_3	H	40
	CF_3	CH_3	CO_2Et	50 [c]
	CH_3	CH_3	CO_2Et	50 [c]
	OMe	CH_3	CO_2Et	50 [c]

product [a, b]

a. reaction conditions are as follows: 1.0 equivalent pyrazole, 2.0 equivalents boronic acid, 3.0 equivalents $Cu(OAc)_2$, 3.0 equivalents pyridine at pyrazole concentration 0.17M in dry CH_2Cl_2
b. regiochemistry determined by nOe difference spectroscopy
c. yield of other regioisomer approx. 30%

Scheme 5.16 N-Arylation of pyrazoles with arylboronic acids.

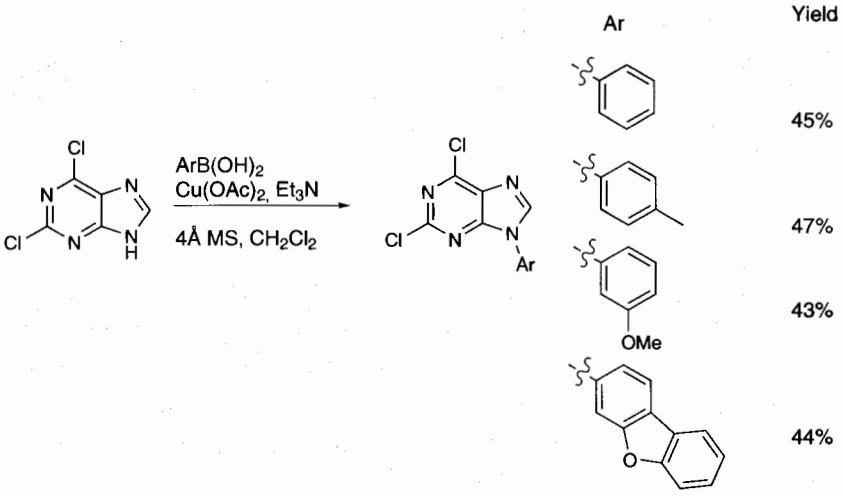




Scheme 5.17 Synthesis of Factor Xa inhibitors.

5.4.2.2 Purines

Purines are important building blocks and scaffolds of biologically active compounds. The copper-promoted N-arylation methodology is applicable to the synthesis of novel N-9-arylated purines. Gray, Schultz and co-workers were the first to report this application (Scheme 5.18) [36]. Reaction of 2,6-dichloropurine with boronic acids in the presence of $Cu(OAc)_2$ and triethylamine resulted in the desired N-9-arylated product as the major regioisomer (>9:1), with the N-7 regioisomer produced in much lower yield.

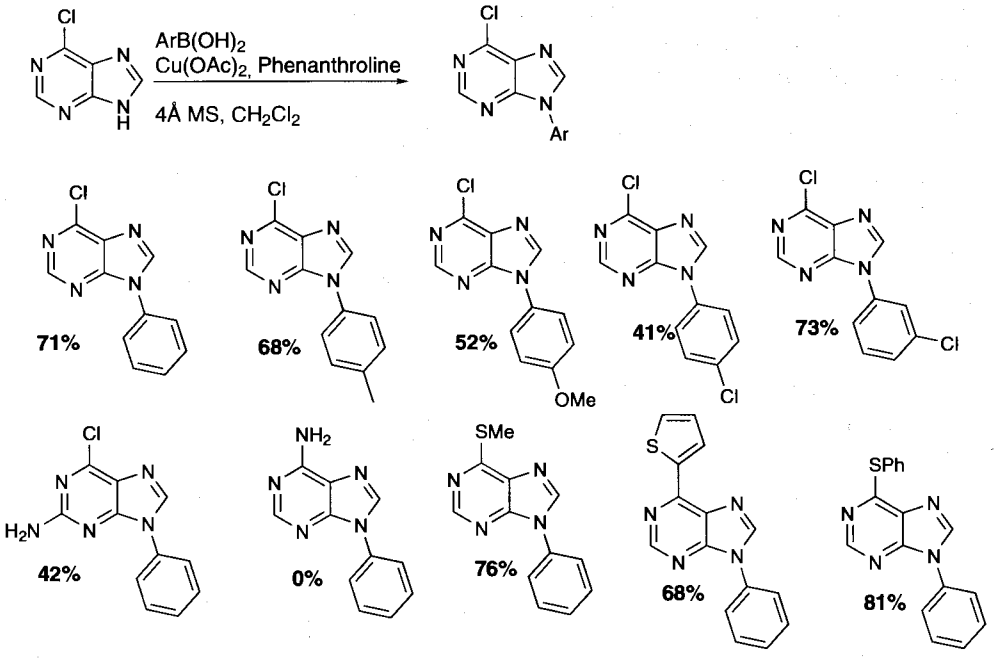


Scheme 5.18 N-9 Arylation of 2,4-dichloropurines.

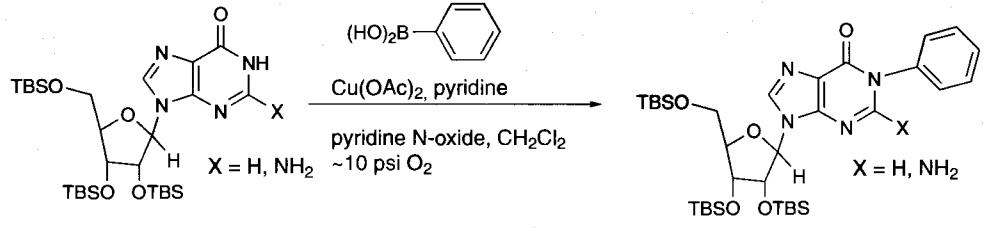
Bakkestuen and Gundersen performed the analogous N-arylation with 6-chloropurines (Scheme 5.19) [37]. The base of choice is phenanthroline, which is superior to 2,2′-dipyridy, TMEDA, and N,N′-diarylethanediimines. Similar to Gray and Schultz's observation, only the N-9 arylated regioisomer was formed, even in the presence of a 2-amino functional group.

Most recently, Strouse, Arterburn and co-workers [38a] presented a preliminary communication (Scheme 5.20) on the N-1 arylation of nucleosides in good yields using Lam's catalytic copper conditions with pyridine N-oxide [38b]. This important application opens the door to arylating many important antiviral nucleosides.

Lam, Richardson and co-workers had also N-arylated various nucleoside bases such as purine, inosine, hypoxanthine and xanthine [39]. The results are listed in the Appendix.



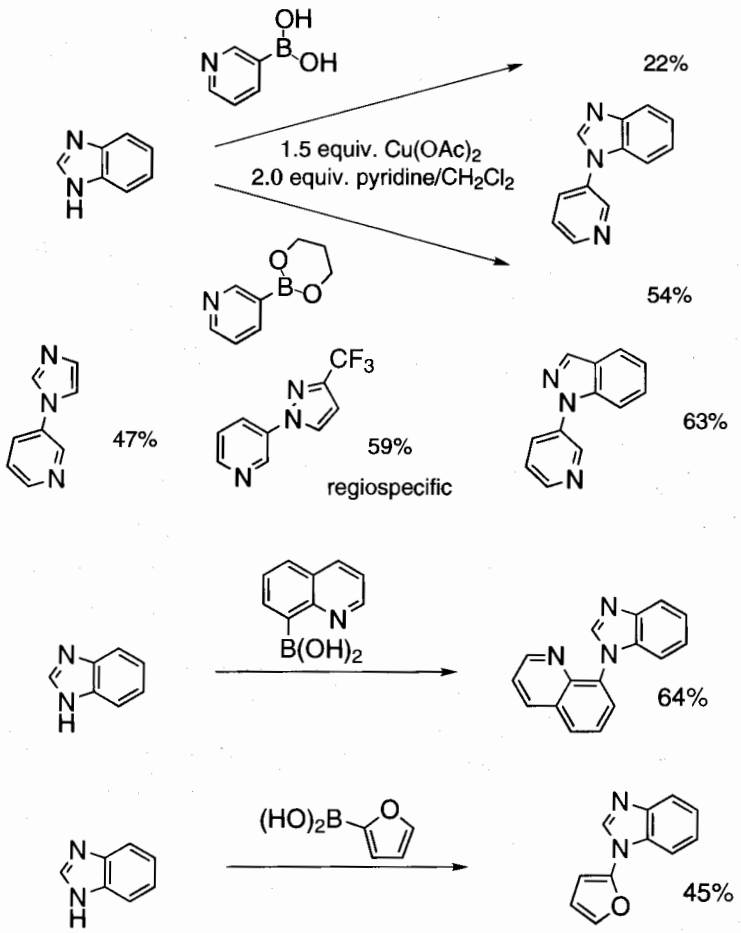
Scheme 5.19 N-9 Arylation of 6-chloropurines.



Scheme 5.20 N-1 Arylation of purine nucleosides.

5.4.2.3 Heteroarene–Heteroarene Cross-coupling

C–N cross-coupling between two heteroarenes is an important process in medicinal, crop-protection, and material science chemistry. Lam and co-workers [10] have explored the cross-coupling between 3-pyridylboronic acid and benzimidazole and obtained only 22% yield. However, changing the boron reagent to the corresponding propylene glycol boronic ester resulted in a higher (54%) yield (Scheme 5.21). Other azoles also gave good yields. 8-Quinolinylboronic acid and 1-furanylboronic acid, conversely, gave 64% and 45% yield with imidazole, respectively [10, 23]. With the report of Quach and Batey [27], these results represent the first demonstrated use of heteroarylboronic acids/esters in N-arylation.

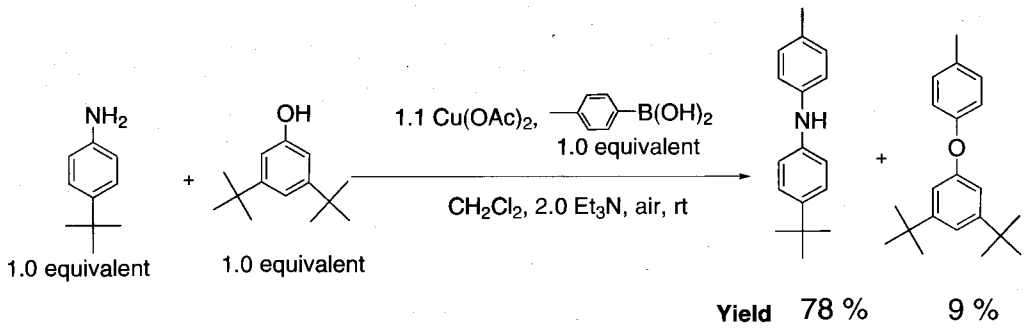


Scheme 5.21 Heteroarene–heteroarene C–N cross-couplings.

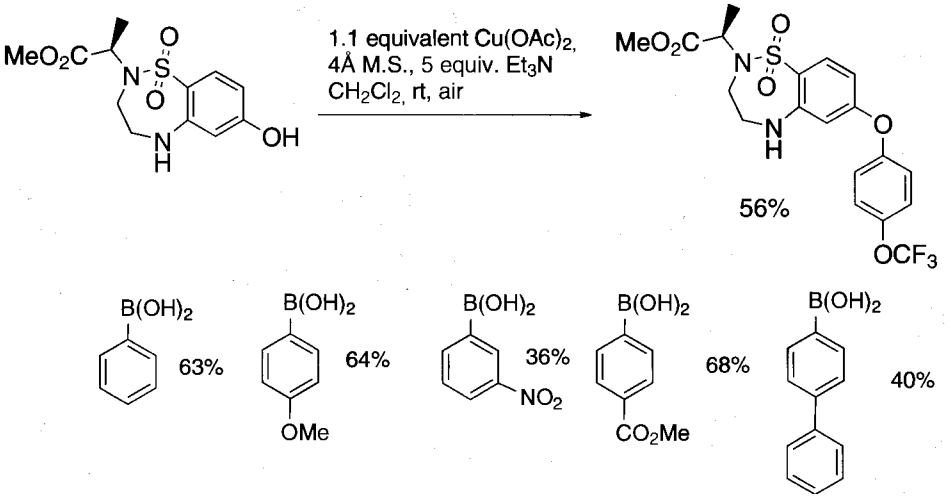
5.5
C–O vs. C–N Cross-couplings

Lam et al. [23] have studied the competition between O- and N-arylation. With 3,5-di-*t*-butylphenol and 4-*t*-butylaniline, N-arylation is nine times faster than O-arylation (Scheme 5.22). Since N-arylation is a faster reaction, the side reaction of arylboronic acid converting into the phenol is probably not as pronounced, and thus the use of molecular sieves may not be necessary (vide infra).

Conversely, in the synthesis of Tumor Necrosis Factor-α Converting Enzyme (TACE) inhibitors, Cherney et al. [40] found that O-arylation occurred in the presence of the more hindered secondary aniline (Scheme 5.23). Arylation of secondary aniline, if it occurred, would have been <5%. This is another example of the copper-promoted N-arylation reaction being very sensitive to steric effects.



Scheme 5.22 Competition experiment of O- vs. N-arylation.



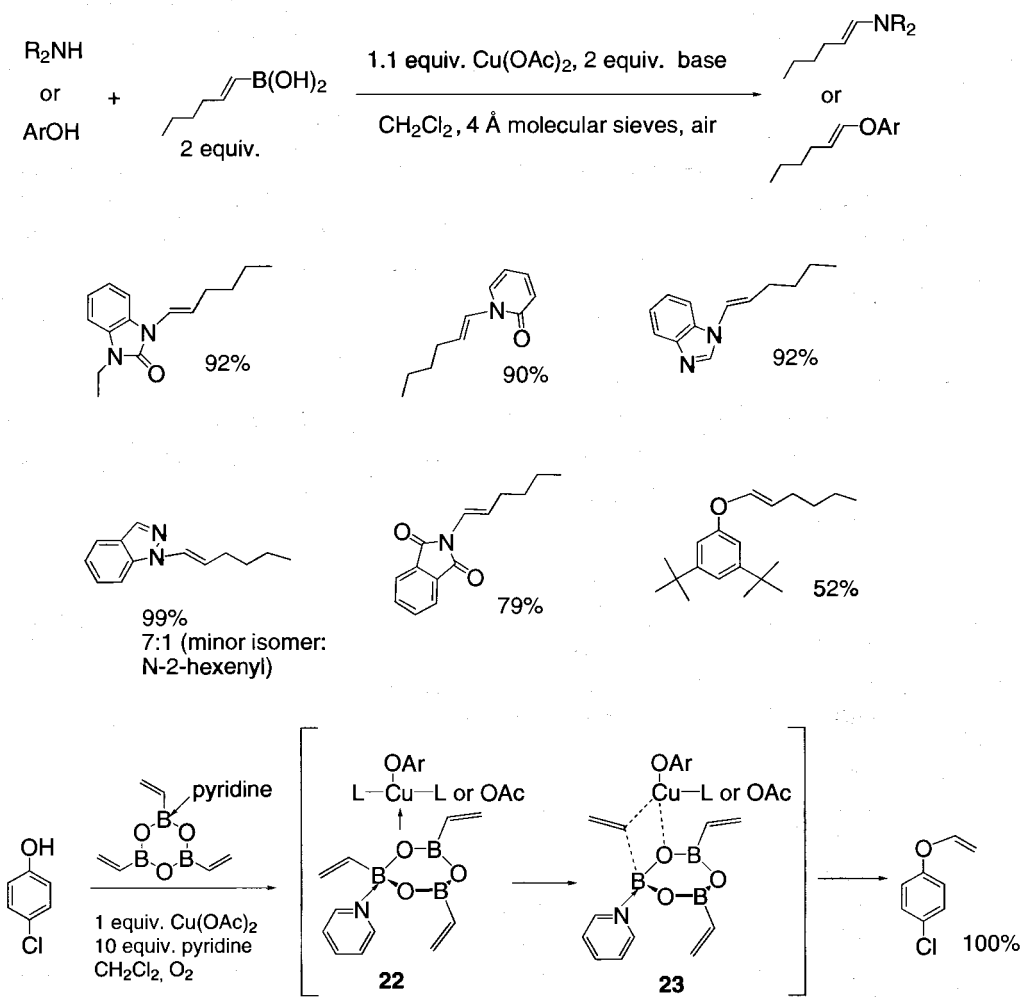
Scheme 5.23 O-Arylation in the presence of secondary anilines.

5.6
C–N and C–O Cross-coupling with Alkenylboronic Acids

There is also a need for a mild N/O-alkenylation reaction. Recent advances by the groups of Ma, Porco, Buchwald, and Willis using copper or palladium catalysts with alkenylhalides or triflates have been reported [41]. However, most substrates still require elevated temperatures. The classical method of enamine formation by azeotroping *n*-hexanal and benzimidazole leads only to the decomposition of the *n*-hexanal. Lam and co-workers [42] discovered that alkenylboronic acids could undergo very efficient copper-promoted alkenylation of N–H or O–H substrates (Scheme 5.24). The reaction can also be run under catalytic conditions, although yields are lower. N-Alkenylamines are useful amine-protecting groups or synthetic intermediates for cyclopropanation and Grubbs metathesis reactions. With a mild method of generating

N-alkenylamines discovered, we expect to see more usage of N-alkenylamine intermediates in the literature.

Recently, McKinley and O'Shea [43] introduced the use of a trivinylboroxine/pyridine complex in place of the unstable vinylboronic acid for O-vinylation (Scheme 5.24). Excess pyridine (10 equiv.) was necessary to obtain high yields. Mechanistic studies revealed the possibility of the formation of intermediate **22**. One postulated function of pyridine is involvement in the conversion of the trigonal boron into "tetrahedral" boron to facilitate the transmetallation of the vinyl group to the copper center (as in transition state **23**). The excess pyridine could be replaced by 1 equiv, of Cs_2CO_3 when the trivinylboroxine/pyridine complex is used. Thus, the second postulated function of pyridine is as a base (vide infra).

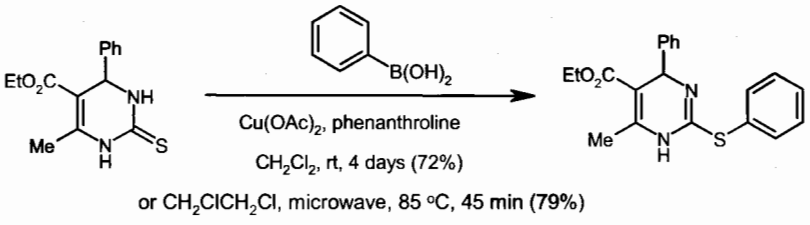


Scheme 5.24 N/O-Vinylation with trivinylboroxine-pyridine.

5.7
C–S Cross-coupling

C–S cross-coupling tends to receive less attention in the literature than C–O and C–N cross-couplings. In Lam's initial studies, no arylation products were observed with 4-t-butylthiophenol and 2-mercaptopyridine using *p*-tolylboronic acid under standard conditions. Guy and co-workers [44] made the first literature report of C–S cross-coupling on the arylation of electron-rich alkyl thiols using standard conditions. Refluxing DMF and an argon atmosphere are required to obtain an optimal yield and to suppress disulfide formation. In a subsequent publication, Liebeskind and co-workers [45] speculated that the reaction may actually involve a Cu(I)-mediated coupling of the boronic acid with the corresponding disulfide since thiols are expected to be rapidly oxidized by the $Cu(OAc)_2$ under the reaction conditions. They then disclosed a mild, non-basic synthesis of thioethers using a Cu(I)-catalyzed C–S cross-coupling of boronic acids with N-thioalkyl-, aryl-, and heteroarylimides. In this case, the imide moiety serves as a sulfide surrogate. Both Guy and Liebeskind's work are discussed in the review by Thomas and Ley [3].

Lengar and Kappe recently reported the arylation of a cyclic thiourea at the sulfur, using phenylboronic acid, $Cu(OAc)_2$ and phenanthroline in dichloromethane at room temperature for 4 days (Scheme 5.25) [46]. The reaction time can be shortened considerably by using microwave irradiation and dichloroethane as solvent, affording similar yields.



Scheme 5.25 S-Arylation with phenylboronic acid.

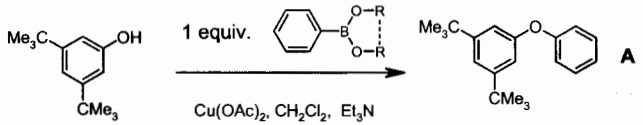
5.8
C–N and C–O Cross-coupling with Boronic Acid Derivatives

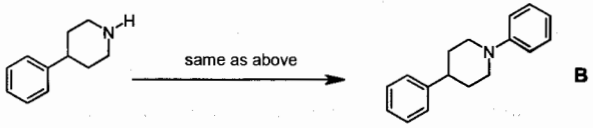
5.8.1
Boroxines, Boronic Esters and Trifluoroborate Salts

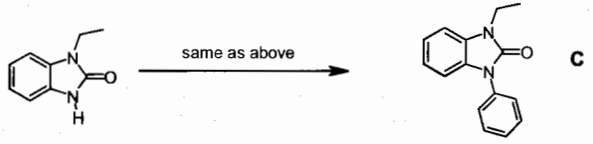
Chan and co-workers have demonstrated that boronic esters can be used in place of boronic acids in both O- and N-arylations in the parent phenyl case (Scheme 5.26) [10]. In both arylations, boronic esters **24**–**27** are even more efficient than the parent acid. However, catechol ester **28** and pinacolate **29** were less efficient, perhaps due to instability (possibility of catechol O-arylation) and steric hindrance respectively. The overall superior performance of the triphenylboroxine (**30**) is noteworthy since it is

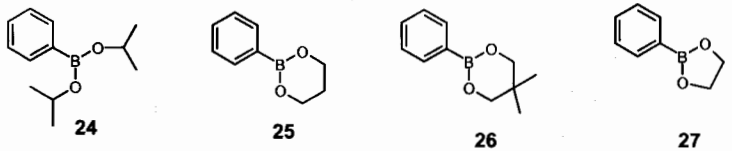
consistent with the early report of Evans [8]. As $PhB(OH)_2$ spontaneously equilibrates to the boroxine form in dichloromethane (vide supra), this result suggests that the active arylating agent in the cross-coupling reactions could indeed be the cyclic anhydride form and not the free acid. One purpose for the addition of molecular sieves could be to promote the formation of the boronic acid. The use of 3-pyridylboronic ester has been discussed in Section 5.4.2.3.

Batey and Quach have investigated alkenyl and aryl trifluoroborate salts as coupling agents. Their earlier publication [47], disclosed a C–O cross-coupling protocol

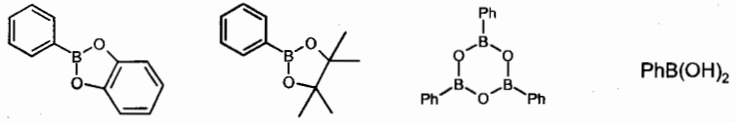








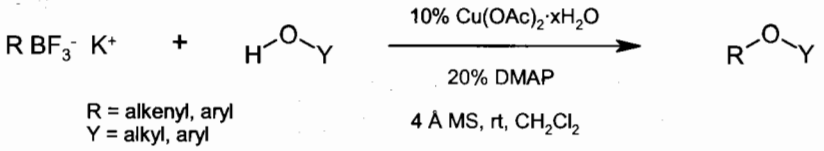
	24	25	26	27
% Yields:	A - 39 B - 29 C - 61	A - 29 B - 42 C - 52	A - 21 B - 43 C - 26	A - 32 B - 30 C - 52



	28	29	30 (0.33 equiv)	
% Yields:	A - 18 B - 28 C - 32	A - 4 B - 23 C - 6	A - 43 B - 40 C - 62	A - 17 B - 22 C - 30

Scheme 5.26 N- and O-Arylation with phenylboronic acid esters.

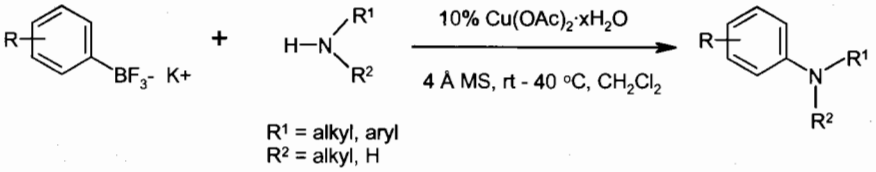
involving catalytic amounts of $Cu(OAc)_2$ and DMAP in the presence of oxygen and molecular sieves (Scheme 5.27). They demonstrated that the fluoroborate salts give better yields than the corresponding boronic acids. Two other interesting aspects of that work are (i) the reaction does not require additional base other than the 20 mol% DMAP used and, perhaps more remarkable, (ii) the chemistry works for aliphatic primary and secondary alcohols. This is the first reported case of alcohols participating in these cross-coupling reactions.



Scheme 5.27 Cu(II)-catalyzed ether synthesis with organotrifluoroborate salts.

A base-free Cu(II)-catalyzed N-arylation using trifluoroarylborate salts has also been reported by the same group (Scheme 5.28) [27]. At the same time they also studied the arylation of primary and secondary amines with phenylboronic acid and discovered that the treatment of 1 equiv. of *n*-$BuNH_2$ or *i*-$PrNH_2$ with $PhB(OH)_2$ (2 equiv.) under typical conditions gave only diphenylamine. Presumably, the initially formed alkylarylamine suffers subsequent Cu-promoted N-dealkylation to give aniline, which then undergoes a second arylation. Interestingly, with only 10 mol% $Cu(OAc)_2$ hydrate as the catalyst and under an oxygen atmosphere, *n*-$BuNH_2$ gave an excellent yield of the monophenylated product with either $PhBF_3^-K^+$ or $PhB(OH)_2$. Generally, phenylboronic acid gave somewhat better yields than $PhBF_3^-K^+$ overall, which is counter to what was observed for C–O cross-coupling.

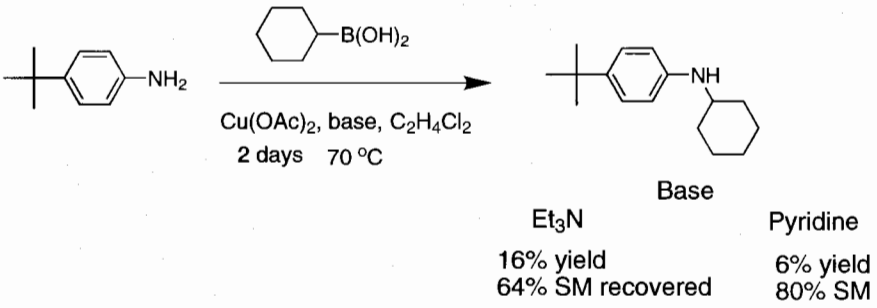
Of the reported procedures for basic alkylamine substrates, the Batey procedure (using arylboronic acids) gave the best yields and is the method of choice.



Scheme 5.28 Cu(II)-catalyzed C–N bond formation with organotrifluoroborate salts.

5.8.2
Alkylboronic Acids

Lam et al. [23a] have also investigated the use of alkylboronic acids. Cyclohexylboronic acid cross-couples with *t*-butylaniline in low yields (16% for TEA and 6% for pyridine) under standard conditions for 2 days at 70 °C in dichloroethane (Scheme 5.29). However, no reaction with phenols or anilines was observed using cyclopropylboronic acid [23a, c].



Scheme 5.29 N-Alkylation with cyclohexylboronic acid.

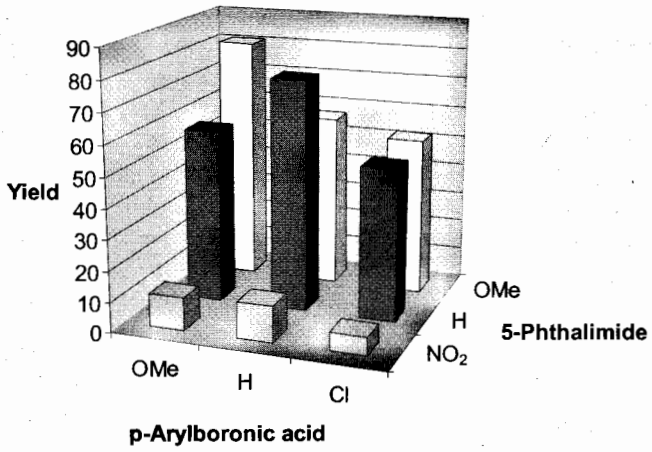
5.9
Mechanistic Considerations

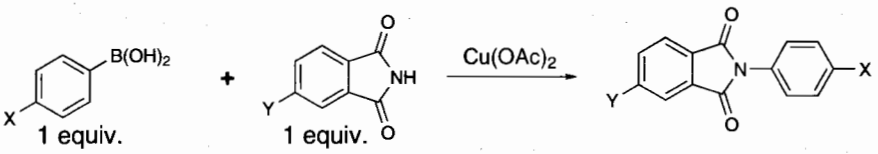
In this section we will attempt to pull together the different aspects of the N/O-arylation reaction in order to shed light on the mechanism of the cross-coupling reaction.

First, this reaction probably does not involve free radicals, as the addition of 1,1-diphenylethylene, a free radical trap, has no effect on the yield of N-arylation of benzimidazole to give *p*-tolylbenzimidazole. Besides, the presence of triplet oxygen will normally intercept the free radicals.

5.9.1
Electronic Effects

Galemmo, Lam and co-workers have studied in detail the electronic effects of the N-arylation of phthalimides with arylboronic acids (Scheme 5.30) [48]. Phthalimide was chosen since it is one of the best substrates for N-arylation. Instead of using the standard amount of excess arylboronic acid, only one equivalent of arylboronic acid was used in order to amplify the electronic effects. Overall there is a strong preference for electron-rich phthalamides but little electronic effects for the arylboronic acid partner. This general trend was also observed for the N-arylation of sulfonamides [48] and azoles [9]. This implies that, in the putative rate-limiting reductive–elimination step (Scheme 5.33 below), Cu–N bond breaking may occur to a larger extent than Cu–C bond breaking.

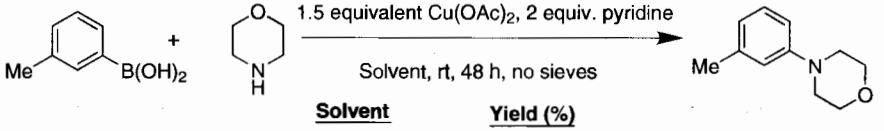




Scheme 5.30 Electronic effect study of boronic acids and phthalimides.

5.9.2 Solvent Effects

A solvent study performed by Combs, Saubern, and Lam, using the N-arylation of morpholine as a prototype (Scheme 5.31) [49], found that methylene chloride and 1,4-dioxane are good solvents. The more polar DMF gave a lower yield. Conversely, for other substrates such as benzimidazole, dimethylformamide has been used (DMF can favor the homocoupled side-product, see Section 5.9.5). Thus the choice of solvent depends on the nature of the substrate. Obviously, the solubility of the Cu(II) salt also has to be considered. Methanol (10 equiv.) additive or refluxing methanol has been used by Snapper, Hoveyda [20] and Xie [26, 50], respectively, to improve yields (Sections 5.3.2, 5.4.1 and 5.4.2).

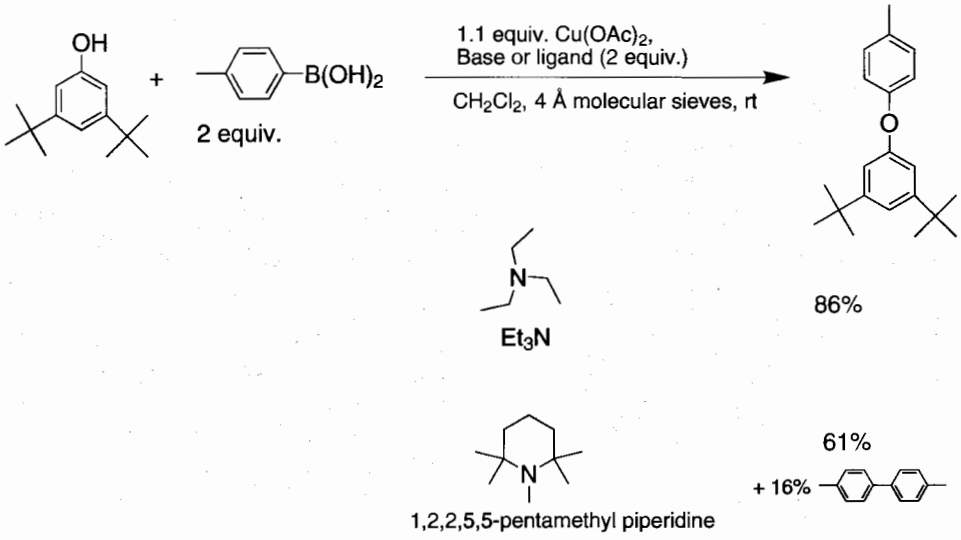


Solvent	Yield (%)
CH_2Cl_2	62
1,4-dioxane	73
DMF	43
EtOAc	26
THF	23
Toluene	18
DMSO	16

Scheme 5.31 Solvent study of N-arylation of morpholine.

5.9.3 Ligand or Base Effects

Lam and co-workers [23b] have studied the role of amine additives since they can function either as a base and/or as a ligand (Scheme 5.32). For O-arylation, the more sterically hindered 1,2,2,5,5-pentamethylpiperidine gave a 25% lower yield than with triethylamine. This 25% component is probably the ligand's contribution of the additive. This suggests that the main role of triethylamine/pyridine is both as a ligand and a base. Interestingly, 4,4′-dimethylbiphenyl was obtained as a side product in 16% yield with the more hindered amine.



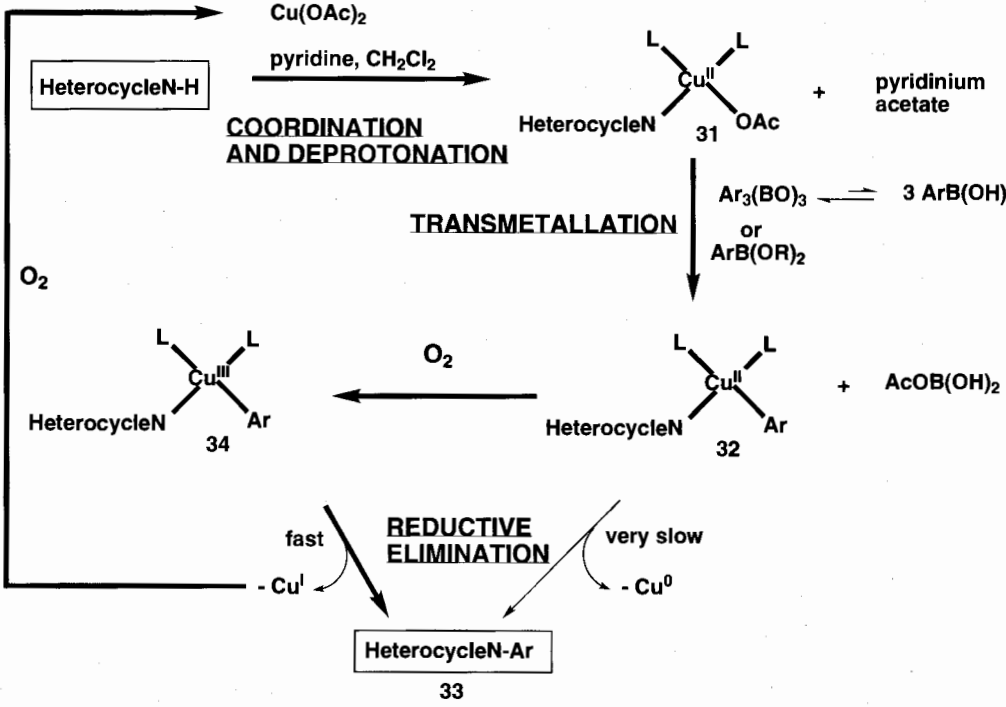
Scheme 5.32 Study on the role of base/ligand.

The ligand effect appears to consist of two opposing components. As described earlier, a large excess of triethylamine reportedly slows the reaction by occupying the free coordination sites at the copper center. However, in the absence of triethylamine, the substrate reacts with arylboronic acid to form the arylboronic acid monoamide adduct, which is less active or inactive [28a].

As discussed in Section 5.3.2, one can suppress protiodeboronation side reactions with the addition of 5 equiv. of DMAP [21]. For N-arylation, the substrates can sometimes serve as base/ligand. Thus no external base/ligand needs to be added in many cases [26]. Conversely, for O-arylation, base/ligand must be used, except for the case of trifluoroborate salts [7, 8, 47].

5.9.4 Mechanism

The authors of this chapter hypothesized that the first step of the reaction mechanism of the catalytic N-arylation of heterocycles with boronic acids involves rapid coordination/ligand exchange and dissolution of copper(II) acetate by the substrate, such as imidazole, to form the complex **31** (Scheme 5.33). This is because cupric acetate is completely insoluble in CH_2Cl_2 (colorless solution), the preferred solvent. When imidazole is added, the solution instantly turns deep blue, suggesting that co-



Scheme 5.33 Possible mechanism for copper-promoted N-arylation.

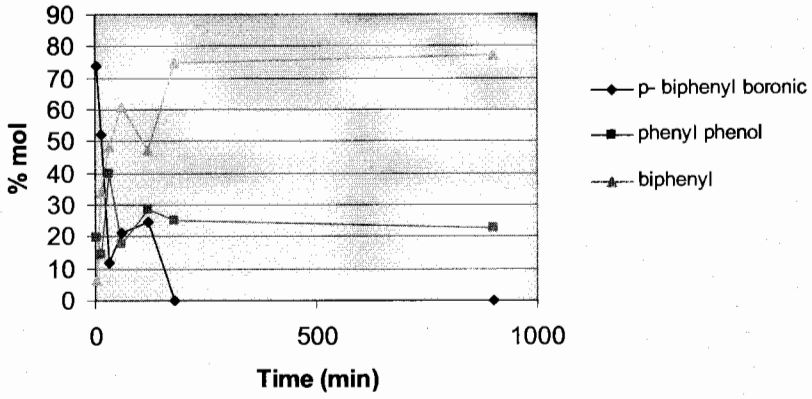
ordination/ligand exchange and dissolution of cupric acetate is the first reaction step. The second step involves transmetallation of the arylboronic acid with **31** to give the imidazole-aryl-copper(II) complex **32**. Complex **32** may undergo reductive elimination to give product **33**, albeit very slowly because imidazole binds to copper very tightly. This step is similar to Buchwald–Hartwig's palladium chemistry and is probably why a high temperature is, in general, needed for the palladium chemistry. Alternatively, **32** is more likely to undergo air oxidation to yield the corresponding higher oxidation-state copper(III) complex **34**, which can now more efficiently reductively eliminate to afford product **33**. When the organometalloid is phenyltrimethoxysiloxane [55] instead of phenylboronic acid, we have titrated for copper(0) and found only trace amount. Presumably, most of the copper at the end of the reaction is in the form of copper(I). Since phenyltrimethoxysiloxane is another form of organometalloid like phenylboronic acid, the same result probably occurs in both cases. Thus, the proposed mechanism is from **32** to **34** to **33**, involving a reactive copper(III) species [8, 16, 51]. Copper(III) species are known [52] and are postulated to be intermediate in the Ullmann reaction. The copper(I) formed can then be easily oxidized by oxygen to copper(II) to complete the catalytic cycle.

5.9.5 Side-products

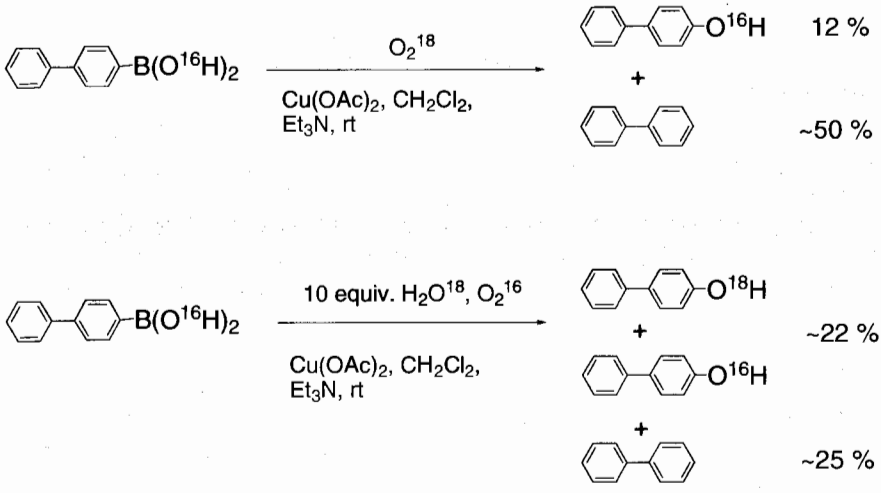
In general, the reaction requires excess arylboronic acid (1.5–2.0 equiv.) since it undergoes side-reactions of protiodeboronation and/or conversion into phenol [8, 51a]. Lam and co-workers found that in the absence of substrates, 4-biphenylboronic acid has a half-life of ≤30 min (Scheme 5.34) [23a]. For the origin of phenol formation, there are two possibilities. Evans and co-workers [8] have speculated that the O-arylation of adventitious water (formed in the arylboronic acid/triarylboroxine equilibrium) is the source of phenol side-product. However, arylboronic acid might be oxidized to phenol via the copper(III) species or the hydrogen peroxide formed as a result of the transformation of oxygen into water. To differentiate between these two mechanisms, a study was performed with labeled O_2 and H_2O in the absence of substrates (Scheme 5.35) [51a]. No ^{18}O incorporation was observed in the isolated phenol using $^{18}O_2$, thus ruling out the oxidation mechanism. When $H_2{}^{18}O$ was used, ^{18}O was incorporated into phenol. Thus these results support the hypothesis of Evans and coworkers [8] that the phenol side-product comes from adventitious water.

For O-arylation, it is critical to employ 4Å molecular sieves to remove water in order to obtain high yields. For the more efficient N-arylation, however, it is not clear whether such sieves are always needed. For example, Scheme 5.36 shows no difference in the yield of product (Entry 3 vs. 7). In fact, excess 4Å molecular sieves can lower the yield of catalytic N-arylation of imidazole with phenylboronic acid. Whereas 4Å molecular sieves (100 mg):imidazole (1 mmol) gave an 81% yield, a ratio of 200 mg:1 mmol gave only a 4% yield [33b].

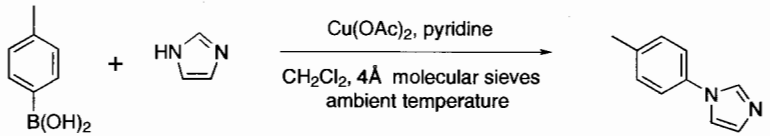
A third potential side reaction is the homo-coupling of arylboronic acid to give the biaryl product (Section 5.9.3) [23a]. This has also been reported recently by Demir et al. [53]. DMF is the preferred solvent to generate more homocoupled biaryl products.



Scheme 5.34 Decomposition of p-biphenylboronic acid in presence of copper(II) acetate and triethylamine. Reaction of biphenylboronic acid in the absence of substrates.



Scheme 5.35 Studies of the source of phenol byproduct.



entry	equiv. boronic acid	equiv. imidazole	equiv. $Cu(OAc)_2$	equiv. pyridine	4Å molecular sieves used	% yield
1	2	1	1.5	solvent	yes	61
2	2	1	1.5	5	yes	58
3	2	1	1.5	2	yes	57
4	2	1	1.0	2	yes	60
5	2	1	0.1	2	yes	<5
6	2	1	2.0	2	no	50
7	2	1	1.5	2	no	58

Scheme 5.36 Molecular sieves and base/ligand studies.

5.10
Other Organometalloids

Arylboronic acid is the most versatile organometalloid due to its efficiency and ready commercial availability. Other organometalloids that can also participate in this copper-promoted cross-coupling reaction are aryltrialkylsiloxanes [51b, 54], aryltrimethylstannanes [55], triarylbismuths [5, 56], arylleads [57], diaryliodonium salts [58a], diethylzinc [58b] and dialkylaluminum chlorides [58c].

5.11
Conclusion

It is interesting to contrast the Chan–Lam copper-promoted C–heteroatom cross-coupling chemistry with that of Buchwald–Hartwig's palladium catalyzed C–heteroatom cross-coupling using aryl halides (Scheme 5.37). Clearly, both methods have positive and negative attributes. The palladium chemistry starts with more cost-effective aryl halides, whereas the copper chemistry uses arylboronic acids that often have to be derived from the corresponding aryl halides. This point is particularly relevant for large-scale production. However, the Buchwald–Hartwig chemistry has yet to be used in any manufacturing processes. For discovery chemistry, this is most often not an issue since there is an abundance of arylboronic acids available commercially [1]. The substrate scopes of these methods overlap a lot. For carbamates and amides, the preferred method is palladium chemistry. For azoles and imides, the copper chemistry has the advantage. Notably, Ullmann coupling still remains a viable alternative, as re-

cent improvements by Buchwald and others [3, 59] have allowed some substrates to be reacted at 80 °C.

Buchwald-Hartwig Pd chemistry	Chan-Lam Cu chemistry
- either ~100°C or *t*-BuONa as base	- rt and weak base
- nitrogen atmosphere	- air
- amines, anilines, carbamates, amides, sulfonamides, phenols, alcohols, thiols	- amines, anilines, azoles, urea, picolinamide, imides, sulfonamides, phenols, alcohol (Batey), thiols (Liebeskind).
- excellent yields	- reasonable to excellent yields
- cheap aryl halides	- aryl/vinyl boronic acids > siloxanes = stannanes; aryl iodides
- catalytic	- mostly catalytic
- Pd expensive	- Cu very cheap

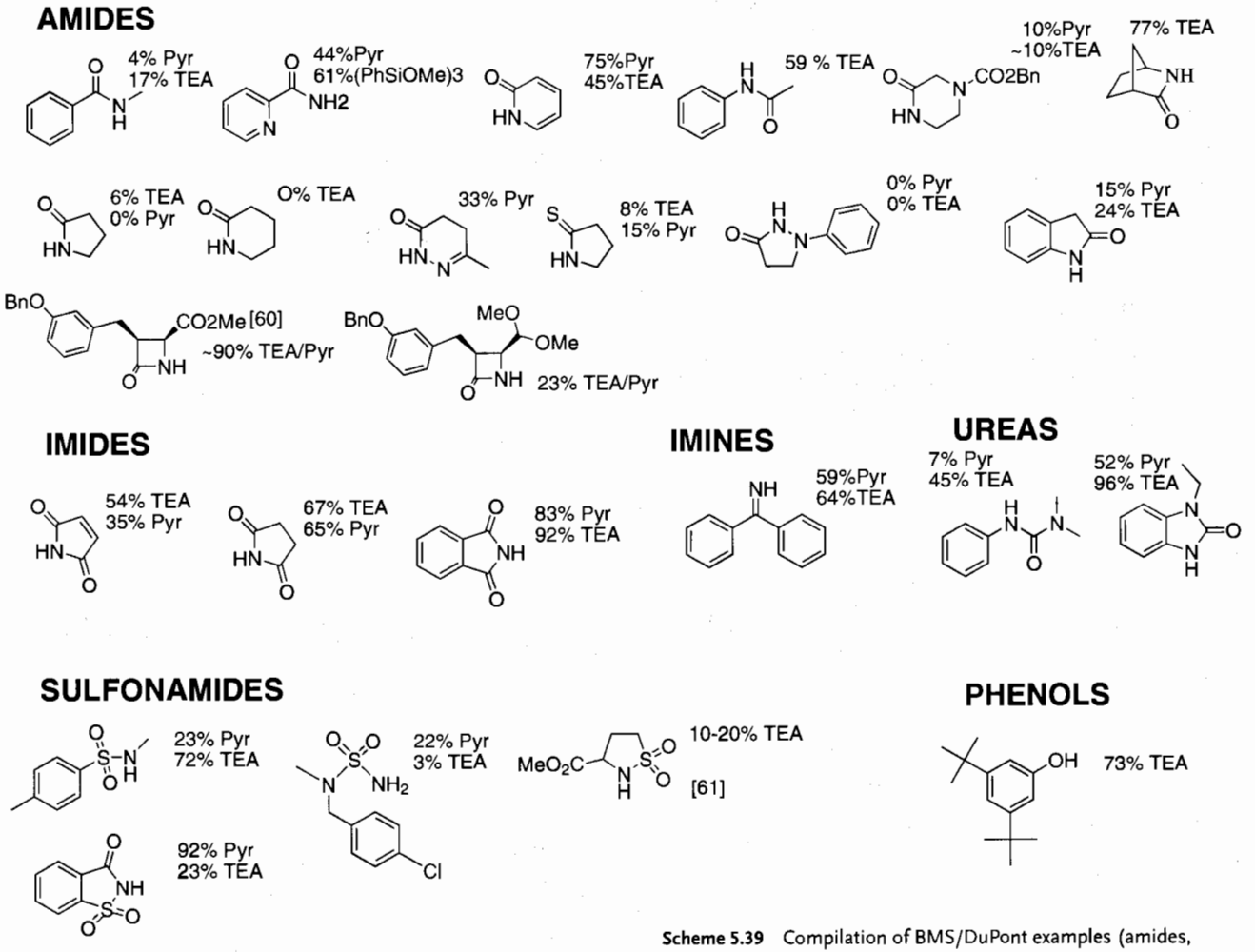
Scheme 5.37 Comparison of C-heteroatom cross-coupling methodologies.

Copper-promoted boronic acid cross-coupling chemistry has come a long way since its invention almost ten years ago. As presented in this chapter, much progress has been made in expanding the scope and in fine-tuning the reaction conditions. Although some questions remain unanswered, this is now a powerful new synthetic tool, particularly for analoging programs in pharmaceutical and crop protection areas where expedient methodologies are in high demand. The copper-promoted C–heteroatom cross-coupling reaction could become as important and useful as the palladium-catalyzed Suzuki–Miyaura C–C cross-coupling reaction.

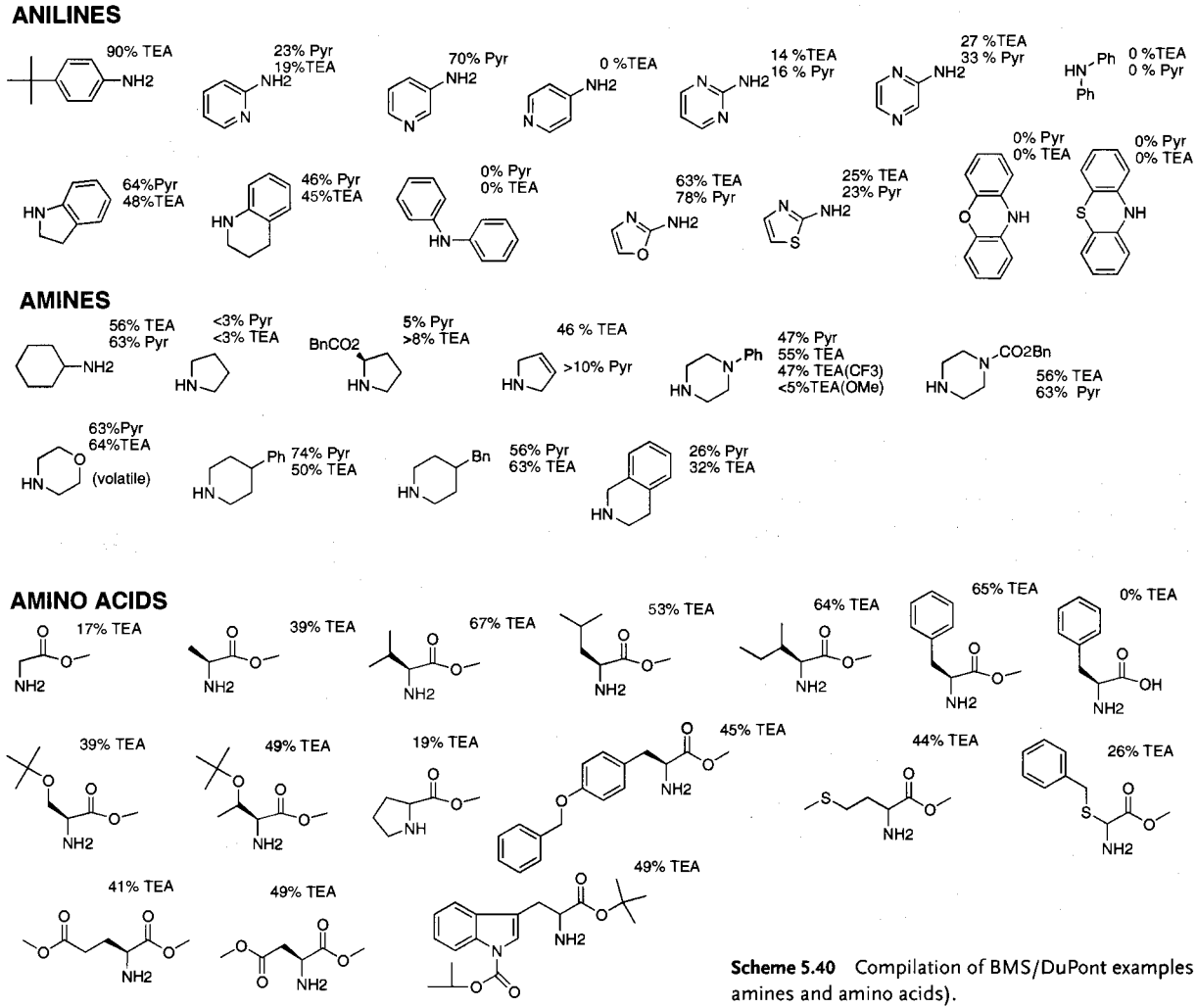
5.12
Appendix

Schemes 5.38–5.40 are compilations of N/O-arylation examples from BMS and DuPont. Many of the yields are not optimized.

Scheme 5.38 Compilation of BMS/DuPont examples (heteroarenes).



Scheme 5.39 Compilation of BMS/DuPont examples (amides, imides, imines, ureas, sulfonamides and phenols).



Scheme 5.40 Compilation of BMS/DuPont examples (anilines, amines and amino acids).

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6
Recent Advances in the Preparation of Allylboronates and Their Use in Tandem Reactions with Carbonyl Compounds

Jason W. J. Kennedy and Dennis G. Hall

6.1
Introduction

Allylboronates have gained a prominent position as a useful class of synthetic intermediates in the past 25 years. Figure 6.1 shows the general structure of allylboronates (**1**). The main use of these reagents is in the stereoselective synthesis of homoallylic secondary alcohols by an allyl transfer reaction to aldehydes (Section 6.3.1) [1–6].

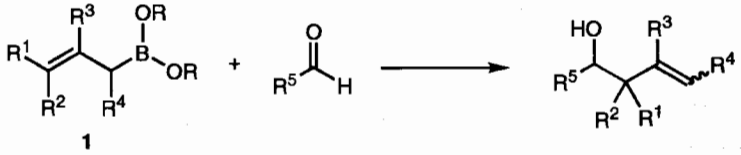

Figure 6.1 Generic structure of allylboronates (**1**) and their addition to aldehydes to provide homoallylic alcohols.

Allylboronates are more stable to atmospheric oxidation and are thus much easier to handle than the corresponding allylboranes. The stability of the boronate reagents comes from the partial donation of the lone pair of electrons on the oxygen atoms into the empty p-orbital of boron. This mesomeric effect is responsible for the higher field resonance of the boron atom in ^{11}B NMR as well as the lower reactivity towards carbonyl compounds of allylboronates compared to analogous allylboranes (cf., Figure 6.2, allylboronate **2** and allylborane **3**) [7]. Another advantage of allylboronates over other carbonyl allylation agents is the high diastereoselectivity of their additions to aldehydes (Section 6.3.1.1).

A potential pitfall of allylboron compounds is the stereochemical integrity of the reagent – substituted allylboron reagents undergo reversible borotropic rearrangements (e.g., Figure 6.4 below, M = BR_2). These rearrangements are the bane of stereoselective syntheses since they can result in the scrambling of the *E*/*Z* geometry of the reagent. Allylboronates are, to great advantage, much less prone to such re-

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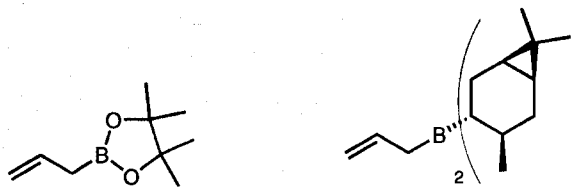
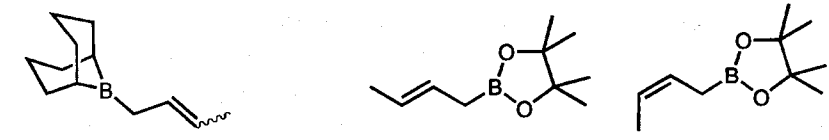


2 **3**

^{11}B NMR: δ 33 ppm (CH_2Cl_2) ^{11}B NMR: δ 82 ppm (THF)

Figure 6.2 Comparison of structures and ^{11}B NMR chemical shifts (200 MHz) of allylboronate **2** and allyldialkylborane **3**.

arrangement than allylboranes. For example, *B*-crotyl-9-BBN (**4**) is a mixture of *E*- and *Z*-isomers at room temperature (Figure 6.3) [8], but the two isomers of pinacol crotylboronate **5** are sufficiently stable at this temperature to independently prepare, isolate, and use [9]. Notably, most pinacol allylbororonic esters are stable to hydrolysis and can be conveniently purified by flash-chromatography on silica gel.



4 ***E*-5** ***Z*-5**

Inseparable *E*/*Z* mixture at room temperature

E/*Z* isomers readily prepared and handled at room temperature

Figure 6.3 Comparison of the stereochemical stability of allylboranes vs. allylboronates.

Several reviews on allylboron compounds and other allylmetal reagents and their additions to carbonyl compounds and imines have appeared [1–6], including two excellent chapters in a book from Wiley-VCH [1, 2]. Accordingly, this chapter does not aim to provide a comprehensive account on the chemistry of allylboronates, but presents instead an overview of the main preparative methods for allylboronates, with particular focus on advances reported in the past five years, and on several recent synthetic applications such as the Lewis acid-catalyzed additions to carbonyl compounds and tandem allylation reactions.

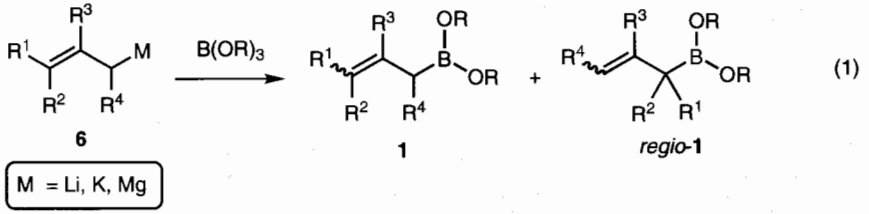
6.2
Preparation of Allylboronates

There are several methods for the preparation of allylboronates, and many of these have been developed in the past decade. In this section, preparative methods are organized according to whether the boronate group is introduced directly to an organic fragment (direct methods) or whether an organoboronate is modified to introduce the allyl group (indirect or "unmasking" methods).

6.2.1
Direct Methods

6.2.1.1 Allylboronates from Allylmetal Intermediates

Among the most common preparations of allylboronates (**1**) is the addition of a reactive allylmetal (**6**) to a borate ester (Equation 1). Preparations from allyllithium reagents [10–14], allyl Grignards [10, 16] and allylpotassium [9, 14, 15, 17–21] species are all well known. This method is popular because the required anions are quite easy to prepare, and because it generally leads to high product yields.



One potential drawback to this approach is that the allylmetal precursor may not be stereochemically stable and may be subject to facile metallotropic rearrangement leading to either regioisomers or *E*/*Z* stereoisomerism (Figure 6.4) [22–24]. Another potential problem is that these preparations often require harsh conditions and the intermediacy of very reactive allylmetals – situations that can lead to incompatibilities with many functional groups. While these impediments constitute no real problem for simple allyl groups [25] or for the simple crotylboronates [9, 17, 18], they can lead to poor regio- and stereoselectivities in more substituted examples. Exceptionally, as shown with the diisopropyl tartrate (DIPT) derivatives (*E*)-**7** and (*Z*)-**7** of Equations (2) and (3) [17], the use of Schlosser's conditions [26] to prepare the configurationally stable crotylpotassium anions allows the preparation of both (*E*)- and (*Z*)-crotylboronates with very high selectivity from the respective (*E*)- and (*Z*)-butene. This approach remains the method of choice for preparing these popular crotylboronate reagents.

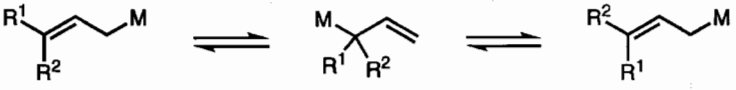
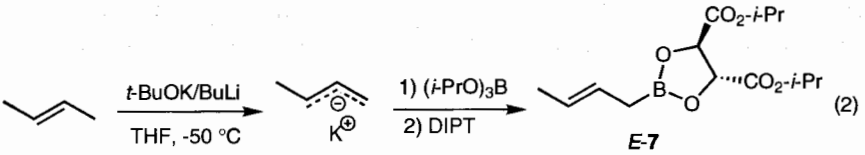


Figure 6.4 Metallotropic rearrangement of allylmetal compounds.



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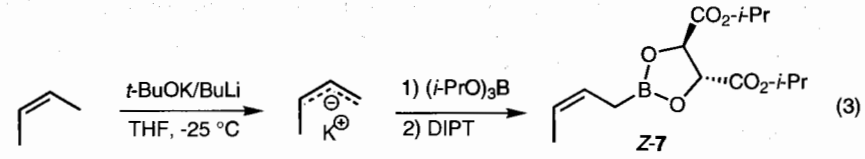
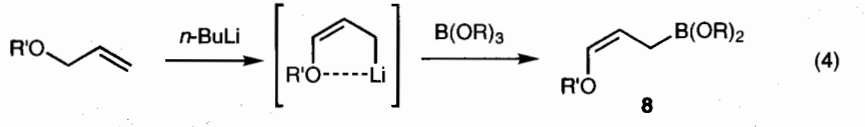


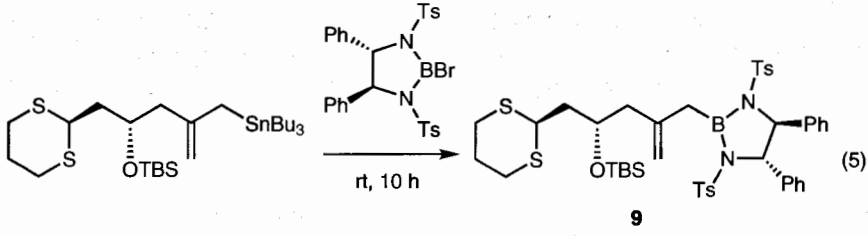
(3)

Several functionalized allylboronates can be made using allylmetal intermediates, including the (*E*)-3-trialkylsilyl ones [27] and the useful (*Z*)-3-alkoxy substituted reagents of type **8** (Equation 4) [28].



(4)

If the presence of sensitive functional groups poses problems of chemoselectivity in the use of hard allylmetal reagents, allylboronate derivatives can also be accessed by transmetallation of allyltin species with boron halides [29]. This approach was used by Corey in the synthesis of chiral bis(sulfonamido)boron reagents (Section 6.3.1.3) [30]. Recently, Williams and co-workers employed this mild approach to synthesize the highly functionalized allylboron reagent **9**, which was employed in a key aldehyde allylboration reaction en route to the total synthesis of leucasdandrolide A (Equation 5) [31].

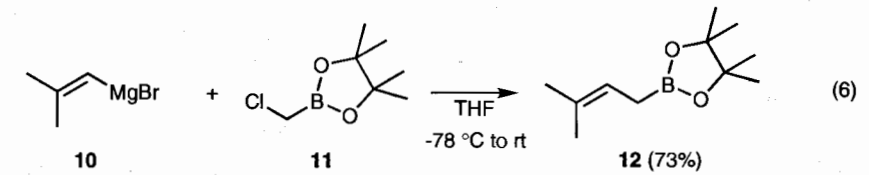


(5)

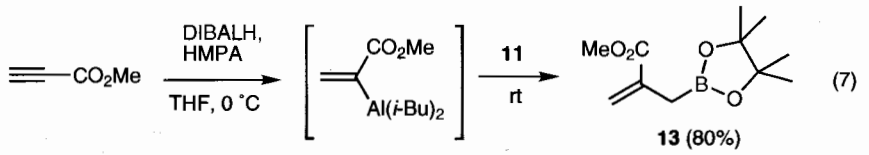
6.2.1.2 Allylboronates from Alkenylmetal Intermediates

As first demonstrated by Wuts and co-workers, the reaction of an alkenylmetal anion with a halomethaneboronate also leads to allylboronates [32]. For example, Grignard reagent **10** reacts with chloromethaneboronate **11** to give the prenylboronate **12** in good yield (Equation 6) [33]. Alkenylmetal reagents are generally more configura-

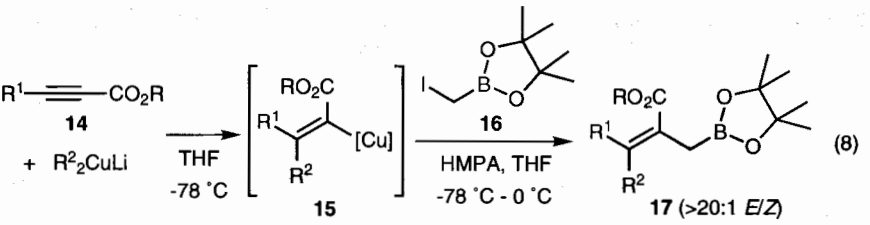
tionally stable than allylmetal species and so alkylations with these anions are usually more stereoselective than with allyl anions. However, the low reactivity of many alkenylmetal species can sometimes bring about poor yields in the alkylation. While the reactions of alkenyllithium [34–36] and alkenylmagnesium [33] reagents with halomethaneboronates are well established, the high reactivity of these organometallics limits the type of functional groups that may be present. In this regard, less reactive alkenylaluminum [37, 38] (Equation 7) and alkenylcopper [39, 40] reagents (Equation 8) have been used to produce more sensitive, functionalized allylboronates such as the 2-carboxyester allylboronates **13** and **17** from alkyne precursors.



(6)



(7)

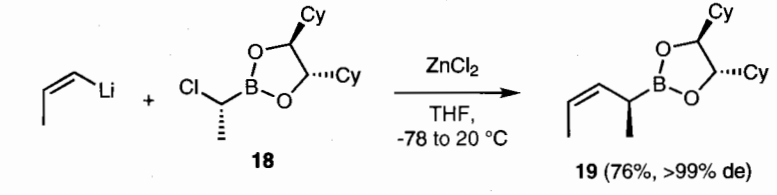


(8)

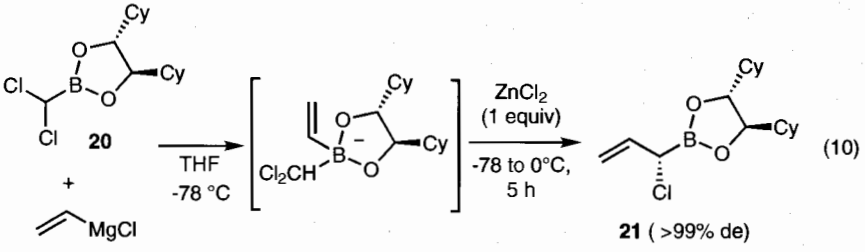
In the last example, cis-carbocupration of alkynoic ester **14** provides a weakly nucleophilic and configurationally unstable 1-alkoxycarbonyl alkenylcopper intermediate (**15**); the presence of HMPA as additive was crucial to avoid erosion of the *E*/*Z* stereoselectivity in the alkylation step with electrophile **16** [39, 40]. Under these conditions, 3,3-disubstituted allylboronates **17** were prepared in over 20:1 selectivity, and these reagents were subsequently employed in the stereoselective preparation of quaternary carbon centers (Section 6.4.2.2).

The use of optically pure α-chloroalkyl boronic esters as electrophiles, e.g. the dicyclohexyl boronate **18** obtained from Matteson's elegant methodology [41], lends access to α-alkyl substituted allylboronates (e.g., **19**) with very high diastereomeric purity by way of a net inversion of configuration (Equation 9) [42]. Likewise, alkenylmetal fragments react with chiral dichloromethylboronate **20** to afford optically pure α-chloroallylboronates such as **21** (Equation 10) [43]. Subsequent addition of these α-substituted reagents to aldehydes is highly stereoselective. Furthermore, the chloride

substituent of these allylboronates can be displaced with various nucleophiles including metal alkoxides and alkylmetal reagents to provide other useful allylation reagents (Section 6.3.1.3).



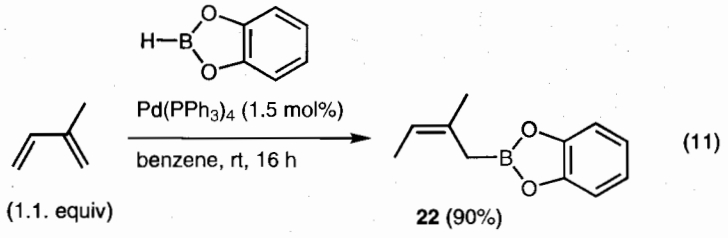
(9)



(10)

6.2.1.3 Allylboronates from the Hydroboration of 1,3-Butadienes and Allenes

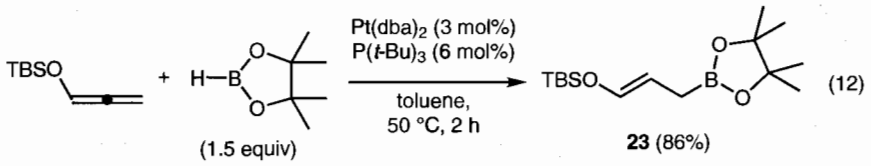
This method has not yet found widespread use for the preparation of allylboronates. In fact, uncatalyzed hydroborations of dienes tend to provide the undesired regioisomer with the boron atom on a terminal carbon, i.e., homoallylic boranes. By making use of certain transition metal catalysts, however, Suzuki and co-workers found that (*Z*)-allylic catecholboronates such as **22** can be obtained in high yield from various substituted butadienes (e.g., isoprene, Equation 11) [44]. Whereas a palladium catalyst is the preferred choice for acyclic dienes, a rhodium catalyst ($Rh_4(CO)_{12}$) was best for the hydroboration of cyclohexadiene. A suitable mechanism was proposed to explain the high regioselectivity of this process. In all cases, a reaction quench with benzaldehyde afforded the expected homoallylic alcohol product from a tandem hydroboration/allylation (Section 6.4.1.4).



(11)

As exemplified with **23**, the highly regioselective platinum-catalyzed hydroboration of alkoxy-substituted allenes with pinacolborane provided the corresponding (*Z*)-γ-alkoxyallylboronates by total anti-Markovnikov addition at the terminal double bond (Equation 12) [45]. Alkyl- and aryl-substituted allenes devoid of an alkoxy group, how-

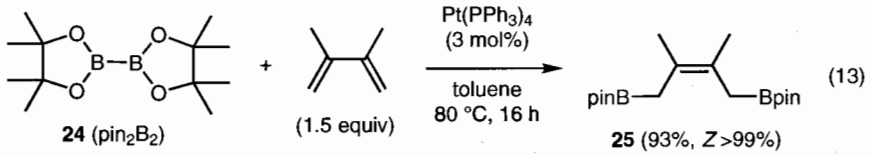
ever, lead to a different regioselectivity and afforded alkenylboronates as major products.



(12)

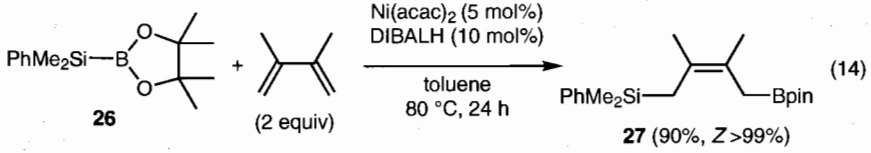
6.2.1.4 Allylboronates from the Transition-metal Catalyzed Diboration and Silaboration of Dienes and Allenes

The ability of the diboronyl reagents to undergo transition-metal catalyzed additions onto unsaturations has been put to use in the preparation of allylboronates. For example, Miyaura and co-workers described the formation of bis(allylboronates) like **25** by diboration of symmetrical dienes with reagent **24** under platinum catalysis (Equation 13) [46]. Norman and co-workers applied this process to the coupling between chiral diboronyl reagents and 1-substituted-1,3-butadienes [47]. Although high yields and clean conversions were observed, the diastereoselectivity in the formation of chiral 1-substituted allylboronates was very low.

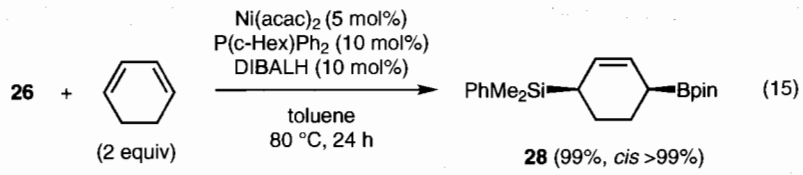


(13)

Ito and co-workers developed the corresponding silaboration process, first using platinum catalysts [48]. Thereafter, the same group found that, in the presence of a nickel catalyst, (dimethylphenylsilyl)pinacolborane (**26**) adds stereoselectively to acyclic 1,3-dienes to give (*Z*)-4-boronyl-1-silyl-2-alkenes such as **27** (Equation 14) [49]. Cyclic 1,3-dienes require slightly different conditions and afford the expected product (e.g. **28**) in high yield and high stereoselectivity (Equation 15). All of these transformations have been exploited in one-pot tandem diboration(silaboration)/carbonyl allylboration reactions (Section 6.4.1.5).

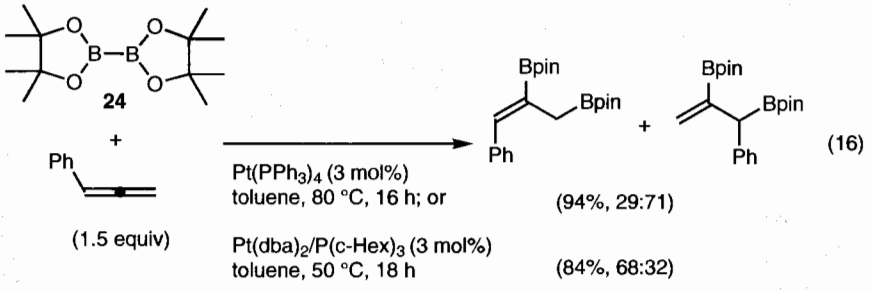


(14)



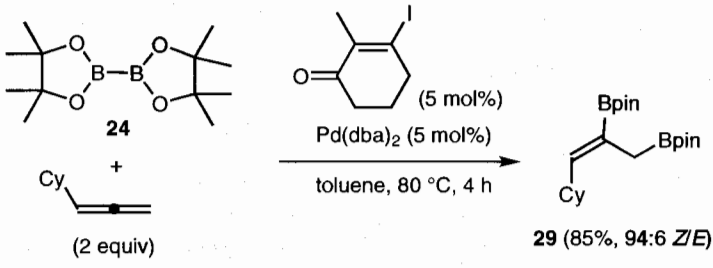
(15)

The Miyaura group similarly applied the diboration process to allenes, and found that the regioselectivity depended highly on the specific conditions used, in particular the presence or absence of a bulky phosphine ligand (Equation 16) [50].



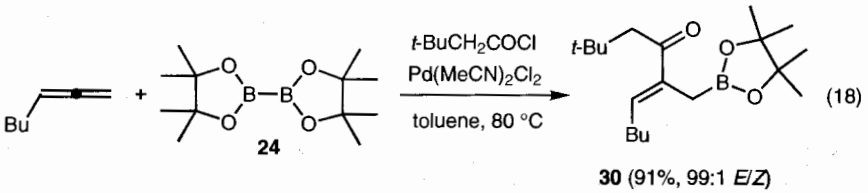
(16)

Yang and Cheng observed an unusual variant of allene diborylation where an aryl or alkenyl halide can act as a co-catalyst with a phosphine-free palladium catalyst [51]. As shown with the formation of allylboronate **29**, the addition is completely regioselective and highly stereoselective (Equation 17). Examples with aryloxy-substituted allenes were also successfully demonstrated. Notably, $Pd(dba)_2$ does not promote the diboration of allenes without the co-catalyst, and a new mechanism involving oxidative addition of an I–B bond to the palladium center was proposed to rationalize these observations.



(17)

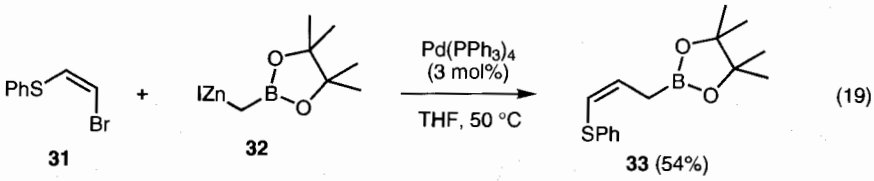
The same group also reported a novel route to tri- and tetrasubstituted allylboronates from acid chlorides, allenes, and diboronyl reagents that proceeds via a palladium-allyl complex (Equation 18) [52]. This method allows for the preparation of a wide variety of highly substituted allylboronates with excellent levels of stereoselectivity. Unfortunately, the stereoselectivity derives from the relative sizes of the two groups at the terminus of the allene, and thus only *gem*-dimethyl tetrasubstituted allylboronates (e.g., where there is no difference in the two groups), and *E*-trisubstituted allylboronates (e.g., **30**, where the difference is very large) have been prepared using this chemistry. Surprisingly, the reaction of these allylboronates with aldehydes has not yet been reported.



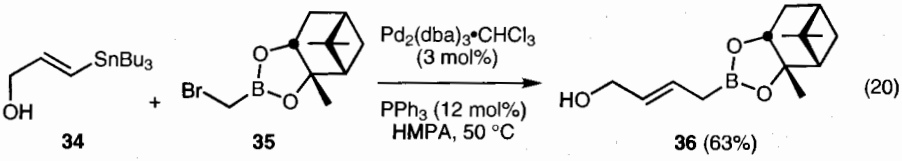
30 (91%, 99:1 *E/Z*)

6.2.1.5 Allylboronates from Palladium-catalyzed Cross-coupling Reactions with Alkenyl Fragments

Allylboronates can also be prepared by palladium-catalyzed cross-coupling reactions involving suitably functionalized alkene substrates. For example, both Negishi coupling [53, 54] between an alkenyl halide, **31**, and Knochel's borylmethylzinc reagent **32** (Equation 19) [55], as well as Stille coupling [56] between alkenylstannane **34** and halomethaneboronate **35** (Equation 20) afforded good yields of allylboronates **33** and **36** respectively. These preparations are complementary in that the boron-containing fragment contains the transition metal in the Negishi coupling, but is the halide-bearing partner in the Stille coupling. Both reactions preserve the *E*/*Z* stereochemistry of the olefin partner and show remarkable functional group tolerance. The presence of an unprotected alcohol in Equation 20 is especially noteworthy.



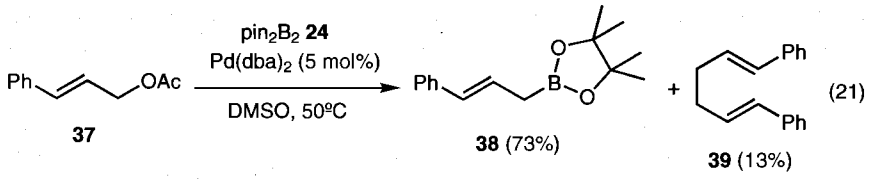
33 (54%)



36 (63%)

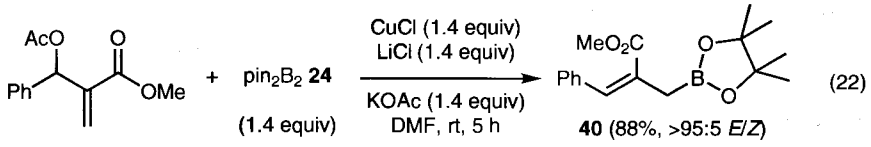
6.2.1.6 Allylboronates from Palladium-catalyzed Cross-coupling Reactions with Allyl Electrophiles

Palladium-catalyzed substitution of an allylic acetate such as **37** with diboronyl reagent **24** gives good yields of allylboronates in DMSO as solvent (Equation 21) [57]. This reaction is a stereoconvergent process; the boron tends to add to the least substituted end of unsymmetrical allylic units, and both *E* and *Z* isomers of acetate **37** yield the *E*-isomer of **38**. Another drawback to this process is that the product is often formed with variable yields of the allylic dimer (e.g., **39**). Allylic halides were also employed as substrates with pinacolborane as the borylating agent and a platinum catalyst [58].



Recently, allylic acetates were borylated as the first step of an efficient one-pot procedure for the allylation of aldehydes [59]. Borylation of allylic acetates can also be performed in tandem with an intramolecular allylboration (Section 6.4.1.6).

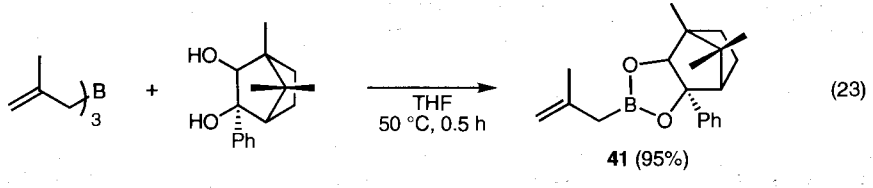
A variant of these reactions was optimized based on the Hosomi–Miyaura borylation of α,β-unsaturated carbonyl compounds with nucleophilic boryl copper, providing 2-alkoxycarbonyl (as well as 2-acyl- and 2-cyano) allylboronates such as **40** in high stereoselectivity (Equation 22) [60]. The resulting 2-alkoxycarbonyl reagents react with aldehydes to provide α-methylene-γ-butyrolactones.



6.2.2 Indirect Methods

6.2.2.1 Allylboronates from Alcoholysis of Triallylboranes

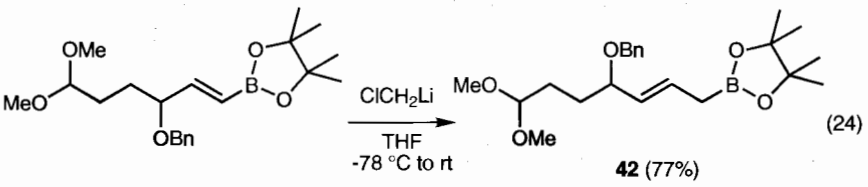
The reaction between triallylboranes and cyclic diols has been scarcely employed, and is limited to the preparation of relatively simple allylboronates like the methallyl reagent **41** (Equation 23) [61, 62].



6.2.2.2 Allylboronates from Homologation of Alkenylboronates

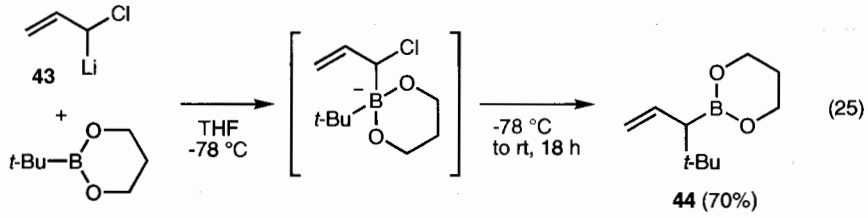
Alkenylboronates can be converted into functionalized allylboronates such as **42** by way of a Matteson homologation (Equation 24) [63–65]. This strategy is the reverse of the addition of alkenylmetal intermediates to halomethylboronates described in Section 6.2.1.2. It is an attractive method because the requisite alkenylboronates are readily prepared by the hydroboration of terminal alkynes. Differentially substituted 3,3-dialkyl allylboronates, a class of reagents that would be difficult to access otherwise, were synthesized using this route [66]. The use of Cl_2CHLi as reagent in this method

allows the preparation of optically enriched α-chloro allylboronates from chiral alkenylboronates [67, 68].



42 (77%) (24)

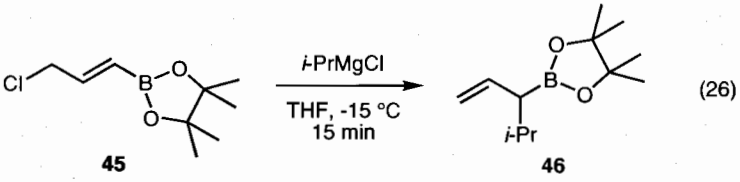
Brown and co-workers employed a related three-carbon variant of the Matteson homologation chemistry to access α-alkyl- and α-aryl allylboronates such as 44 from chloroallylic carbanion 43 (Equation 25) [69].



44 (70%) (25)

6.2.2.3 Allylboronates from Allylic Rearrangement of Alkenylboronates

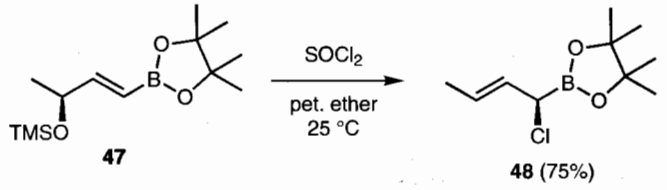
A preparative method similar to the previous one is the vinylogous Matteson rearrangement of pinacol 3-chloroallylboronate (45) exploited by Lombardo and coworkers (Equation 26) [70]. Here, a Grignard reagent adds to 45 with allylic rearrangement to give substituted allylboronate 46. These allylboronates were not isolated but, rather, they were immediately reacted with an aldehyde to give the corresponding homoallylic alcohol product. Although this route holds promise as an efficient entry to various substituted allylboronates, it suffers from a low stereoselectivity in the allylation process.



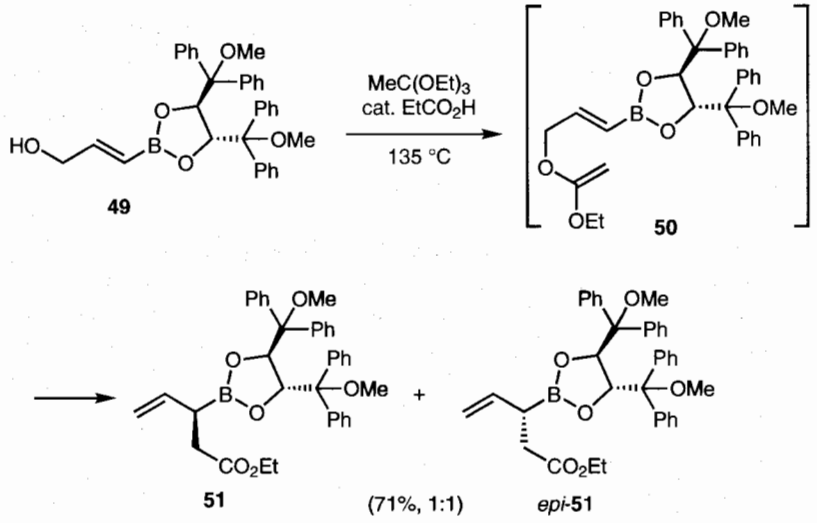
45 **46** (26)

Intramolecular versions of the above allylic substitutions have been developed. For example, Hoffmann and Dresely reported in 1986 that treatment of the optically active γ-siloxyalkenylboronate 47 provides the useful α-chloro-(*E*)-crotylboronate 48 with an almost perfect level of chirality transfer (Equation 27) [71]. Schlapbach and Hoffmann more recently reported the preparation of α-sulfonamido allylboronates by sequential treatment of 47 with $SOCl_2$ and the corresponding lithiated sulfon-

amide anion [72]. Recently, the stereoselective [3,3]-sigmatropic rearrangement of chiral alkenylboronic ester **50** was described [73]. Thus, upon treatment under standard conditions for a Johnson rearrangement, both *E* and *Z* allylic alcohol **49** led to a **1:1** mixture of readily separable diastereomers of α-chiral allylboronate **51** (Equation 28). These reagents were tested in aldehyde addition chemistry and behaved as anticipated to provide homoallylic alcohols in high enantiomeric excess.



(27)

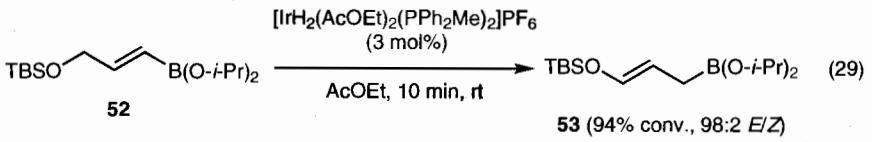


(28)

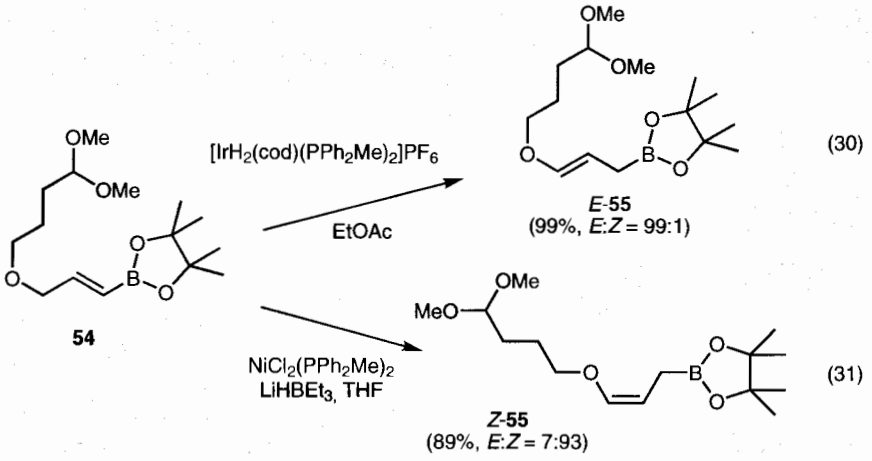
6.2.2.4 Allylboronates from Isomerization of Alkenylboronates

Several ruthenium and iridium complexes can isomerize an alkenylboronate to the corresponding allylboronate by double bond migration [74]. With an iridium catalyst, this process can be effected efficiently and with high *E*/*Z* selectivity for 3-(alkoxymethyl)alkenylboronates. The forward reaction is thought to be favored because of oxygen–alkene conjugation in the resulting enol ether. For example, Miyaura and co-workers prepared the stereochemically pure (*E*)-3-(siloxy)-allylboronate **53** by isomerization of **52** with an iridium catalyst at room temperature (Equation 29) [75]. With ethyl acetate as solvent, the conversion was almost complete, with minimal isomerization to the *Z* isomer of **53**. This diisopropyl ester product was then converted into the useful tartrate boronate by diol exchange. Interestingly, a related ruthenium-catalyzed pinacolboration of propargyl ethers also leads to double bond

isomerization and provides the corresponding (*Z*)-3-(siloxy)allylboronates, albeit with incomplete conversion [76].

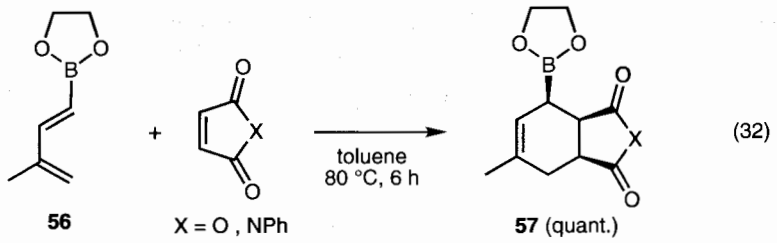


The suitability of these 3-alkoxy-substituted reagents in additions to aldehydes was also examined; this isomerization process was applied in a sequential isomerization/intramolecular allylboration approach to oxygen-containing heterocycles. The required reagents are available by the iridium-catalyzed isomerization of the alkenylboronate **54** to give (*E*)-**55** with excellent selectivity (Equation 30). Use of a nickel catalyst instead of iridium lends access to the opposite isomer, (*Z*)-**55**, albeit in slightly lower selectivity (Equation 31) [77]. Immediately following their isolation, the resulting allylboronates were subjected to a $Yb(OTf)_3$-catalyzed hydrolysis of the acetal, which triggered the intramolecular allylboration (Equation 37, Section 6.3.1.1).



6.2.2.5 Allylboronates by Cycloadditions of Dienylboronates

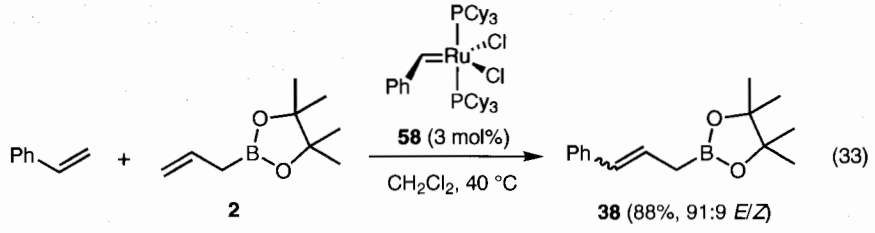
Vaultier and co-workers were the first to demonstrate the utility of 1-borono-1,3-butadienes in [4+2] cycloadditions with electron-poor dienophiles such as maleic anhydride and maleimides (Equation 32) [78]. As exemplified with diene **56**, the [4+2] cycloaddition unmasks an allylboronate, **57**, which at that time was isolated prior to its use in aldehyde allylboration. Lallemand and Six later showed that this sequence can be performed easily as a one-pot, three-component process [79], and the same group used this chemistry as an approach to the synthesis of clerodin [80]. Since then, the one-pot tandem [4+2] cycloaddition/allylboration strategy has been extended to the construction of highly functionalized heterocycles (Section 6.4.1.1).



56 X = O, NPh **57** (quant.) (32)

6.2.2.6 Allylboronates by Olefin Metathesis

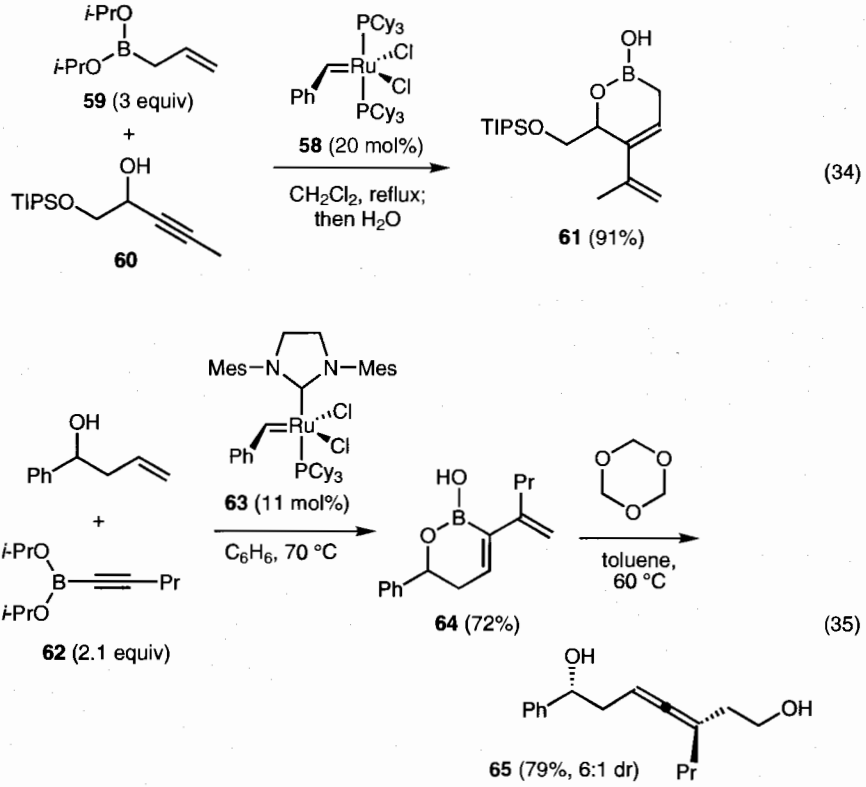
In contrast to the preparative methods described above, a functionalized allylboronate can be created from a simpler allylboronate by olefin cross-metathesis [81, 82]. Here, treatment of pinacol allylboronate (**2**) with various olefin partners, exemplified with styrene in Equation (33), in the presence of ruthenium catalyst **58** smoothly furnishes a more elaborate 3-substituted allylboronate, the cross product **38** [81]. These reactions are noteworthy for their exceptional functional group tolerance; allylboronates bearing primary halides can be directly synthesized using this method. Unfortunately, the *E*/*Z* selectivity in the formation of the 3-substituted allylboronates is variable. This metathesis approach to allylboronates was employed as the beginning of a tandem cross-metathesis/carbonyl allylation process [82] (discussed in more detail in Section 6.4.1.3).



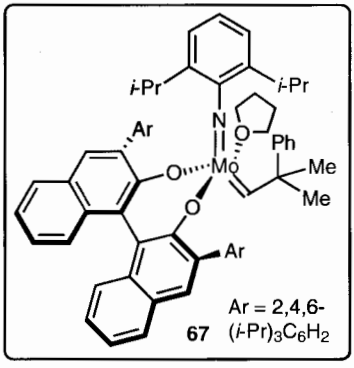
2 **38** (88%, 91:9 *E*/*Z*) (33)

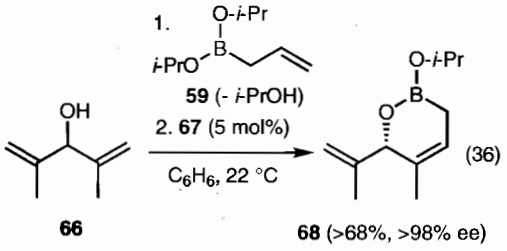
Micalizio and Schreiber have developed a boronic ester annulation based on the transesterification of allylic and propargylic alcohols with diisopropyl allylboronic ester **59** to give the respective allyl and dienyl cyclic boronates (Equation 34) [83]. Thus, in the presence of metathesis catalyst **58**, the transient, mixed boronic ester from the condensation of **59** and **60** undergoes in situ RCM to give the dienylboronic ester **61**. By using alkynylboronates (e.g., **62**), a related ene-yne metathesis process with catalyst **63** led to 2-butadienyl boronates such as **64** (Equation 35) [84]. Although neither preparation has yet been turned into a one-pot tandem process, the crude unpurified product **64** was treated with formaldehyde to generate the allenylation product **65**. This two-step sequence has been realized on solid support and is reported to work with aldehydes, thus demonstrating once more the great synthetic versatility of allylboronate derivatives.

Using the same concept, Hoveyda and co-workers recently employed molybdenum derived chiral complexes to develop a net catalytic enantioselective, cross metathesis process based on either the kinetic resolution of racemic allylic alcohols or the asym-



metric desymmetrization of prochiral bishomoallylic alcohols [85]. For example, condensation between bisallylic alcohol **66** and allylboronate **59** provided the corresponding mixed boronic ester, which was treated with chiral catalyst **67** to give optically pure cyclic allylboronate **68** (Equation 36). The corresponding diol was isolated after oxidation of **68**. Alternatively, this 3,3-disubstituted allylboronate was applied to one example of the formation of a stereogenic quaternary carbon center by allylation of paraformaldehyde.





6.3
Reactions of Allylboronates

6.3.1
Additions to Aldehydes – Formation of Homoallylic Alcohols

Although several classes of carbonyl compounds or their derivatives react with allylboronates (see below), the most common use of allylboronates in synthetic chemistry is their nucleophilic addition to aldehydes to produce secondary homoallylic alcohols (Figure 6.5) [1–6], a process first discovered in 1974 [10].

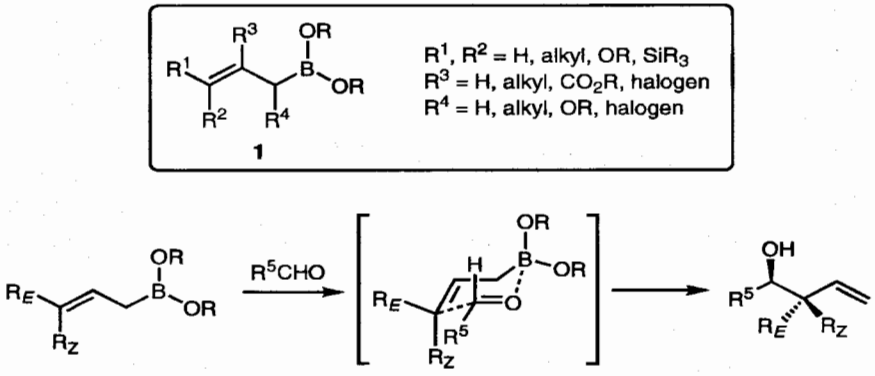


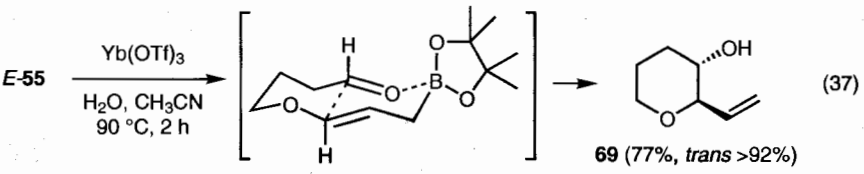
Figure 6.5 General reaction of allylboronates (**1**) with aldehydes via a cyclic chair-like transition state.

Numerous allylboronate derivatives (**1**) with various substituents (R^1–R^4) and boronate ligands have been reported, and interested readers can refer to reviews for a comprehensive compilation of these useful reagents [1, 2].

6.3.1.1 Stereoselectivity and Mechanism of Non-catalyzed Additions

Mechanistically, allylboronates belong to the Type I class of allylating reagents [86, 87]. Although catalytic variants have recently been disclosed (Section 6.3.1.2), an allylboronate and an aldehyde react spontaneously, requiring no external activator. The reaction proceeds by way of a six-membered, chair-like transition state that features a coordination bond between the boron and the carbonyl oxygen of the aldehyde (Figure 6.5) [88]. The strength of this interaction is the most important factor in determining the overall reaction rate [89], and the most reactive allylboronates are those with the most electrophilic boron centers [7]. Thus, allylations with allylboronates (^{11}B $\delta \sim 30$ ppm) are significantly slower than reactions with the analogous allylboranes (^{11}B $\delta \sim 70$ ppm). The nucleophilicity of the γ-position of the allylboronate (the position that forms the new C-C bond with the aldehyde) is also important to the reactivity of the boronate, and substituted allylboronates with groups that reduce electron density at this position (e.g., 2-carboxyesters [38, 39], 3-alkoxy groups [13, 90]) are correspondingly less reactive than similar allylboronates that lack these groups.

One of the main reasons why allylboronates have become such popular tools in stereocontrolled synthesis is that their additions to aldehydes are typically and reliably highly stereoselective. The diastereospecificity of the reaction was first recognized by Hoffmann and Zeiss in 1979 [18]. The allylation generally proceeds with retention of the olefin geometry, with (*E*)-crotylboronates (Figure 6.5, R_E = Me, R_Z = H) leading to *anti*-products and (*Z*)-crotylboronates (Figure 6.5, R_E = H, R_Z = Me) leading to *syn*-products. In both cases, of the two possible chair-like transition states the favored one places the aldehyde substituent (R^5) in a pseudo-equatorial orientation. This model accounts for the diastereoselectivity of most allylborations, and even highly functionalized allylboronates and intramolecular additions follow this trend [91, 92]. For example, the (*E*)- and (*Z*)-allylboronates **55** described in Section 6.2.2.4 provide the respective trans- and cis-fused products of intramolecular allylation [77]. As shown for allylboronate (*E*)-**55**, $Yb(OTf)_3$-catalyzed hydrolysis of the acetal triggered the intramolecular allylboration and led to isolation of the trans-fused product **69** in agreement with the usual cyclic transition structure (Equation 37).



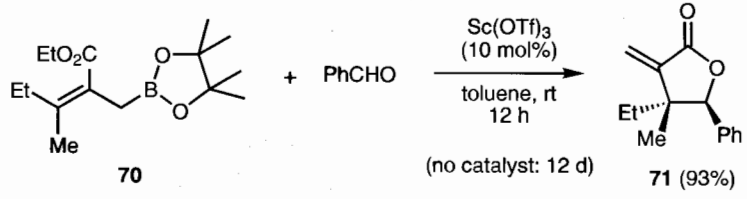
69 (77%, *trans* >92%) (37)

The high stereoselectivity of aldehyde allylboration reactions is a consequence of the compact cyclic transition state. This model accurately predicts the stereochemical outcome of most allylborations, and theoretical calculations have shown that the chair-like transition structure (Figure 6.5) is the lowest energy state relative to other possibilities [88, 93]. It was also suggested that a weak hydrogen bond interaction between the axial boronate oxygen and the hydrogen of the polarized formyl unit contributes to favoring the transition structure with the aldehyde substituent in the pseudo-equatorial position [94]. Unfortunately, the transfer of stereochemistry is not always perfect, suggesting that in some cases other transition states (e.g., boat transition states, chairs with axial aldehyde residues) might be attainable.

6.3.1.2 Lewis Acid-catalyzed Additions

As described above, allylboronates are self-activating, Type I reagents, where the allylation is governed by coordination of the aldehyde carbonyl to the boron atom. Because of this self-activation mechanism, there would appear to be no advantage to using an external promoting agent (e.g., a Lewis acid catalyst). Furthermore, an external Lewis acid might compete with the boron atom for the aldehyde, potentially leading to a switch from the highly diastereoselective Type I mechanism to a less selective, open-chain Type II mechanism. However, recent publications show that these reactions can be efficiently and beneficially catalyzed by several Lewis acids [95–99]. As first reported by Kennedy and Hall, the rate enhancements in the presence of these catalysts are quite dramatic [95]. For example, the addition of 2-carboxyester allylboronates **70** to benzaldehyde to give *exo*-methylene butyrolactones **71** takes almost

two weeks at room temperature, but only 12 h in the presence of a catalytic amount of $Sc(OTf)_3$ (Equation 38) [95]. Note that the initially formed homoallylic alcohol cyclizes in situ with the carboxyester group to form a lactone product in these reactions (Section 6.4.2.2).



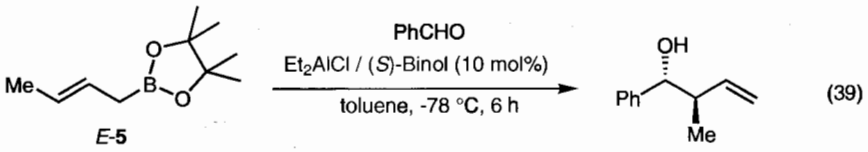
(38)

Notably, the stereospecificity observed in the thermal reaction is preserved under this new catalytic manifold. Furthermore, the 2-alkoxycarbonyl substituent on the allylboronates was not necessary for the metal-promoted activation to occur [95, 96]. From recent mechanistic studies, a chair-like bimolecular transition structure similar to the thermal additions can be proposed for these catalyzed allylborations [100]. According to control experiments that showed the inefficiency of Lewis acids with dialkylallylboranes, the catalytic effect is thought to derive from an increase in the electrophilicity of the boron atom following binding of the metal ion to one of the boronate oxygens (T.S. **A**) as opposed to coordination of the carbonyl oxygen (T.S. **B**) (Figure 6.6) [100]. Indeed, theoretical studies by Omoto and Fujimoto showed that the strength of the coordination bond between the boron and the aldehyde carbonyl in the transition state is the most important rate-determining factor [89]. Thus, coordination of the Lewis acid to the boronate oxygens would disrupt the overlap of the oxygen lone pairs with the empty p-orbital of the boron atom. Consequently, the boron center is rendered more electron deficient, and compensates by strengthening the key boron–carbonyl interaction and, concomitantly, lowering the activation energy of the reaction. This idea stems from the experimental work of Brown and co-workers, who observed, following a quantitative survey of the reactions of different allylboronates, that the rate of a given allylboration can "be rationalized in terms of the relative availability of lone pairs of electrons on the oxygen atoms attached to the boron." [7].

The real promise of this catalytic reaction is the eventual development of an efficient enantioselective allylboration catalyzed by chiral Lewis acids. Currently, the on-

Figure 6.6 Possible transition structures for the Lewis acid-catalyzed allylboration. (A) Coordination of a boronate oxygen. (B) Double coordination of the aldehyde carbonyl.

ly example of a stereoselective reaction using a substoichiometric amount of a chiral director (i.e., true enantioselective catalysis) was reported by Miyaura and co-workers, who achieved modest levels of chiral induction with an aluminum-BINOL catalyst system (Equation 39) [96]. However, excellent levels of stereocontrol can be achieved in the scandium-catalyzed reactions of camphordiol chiral allylboronates (Section 6.3.1.3) [98].



6.3.1.3 Stereoselective Additions with Chiral Allylboronates

The many strategies devised for controlling the absolute stereoselectivity in additions of allylboronates to aldehydes [1–6] can be divided into two general classes of chiral reagents: (1) Allylboronates embodying an α-chiral carbon (C-chiral allylboronates), and (2) allylboronates with a chiral unit on the boron's two heteroatom substituents (B-chiral allylboronates). The latter approach is more popular because it is generally easier to manipulate the boron's heteroatom substituents than it is to make an allylboronate with a chiral carbon. Several examples of both classes of reagents have been reported (Figure 6.7) and reviewed recently [1, 2]. This section will focus on providing an overview of the most popular systems and the emerging ones.

Hoffmann and co-workers reported in 1978 the first examples of chiral allylboronates [61]. These reagents were assembled from rigid camphor-derived 1,2-diols, providing different allylation reagents of generic structure **72** and **73** [62]. Although

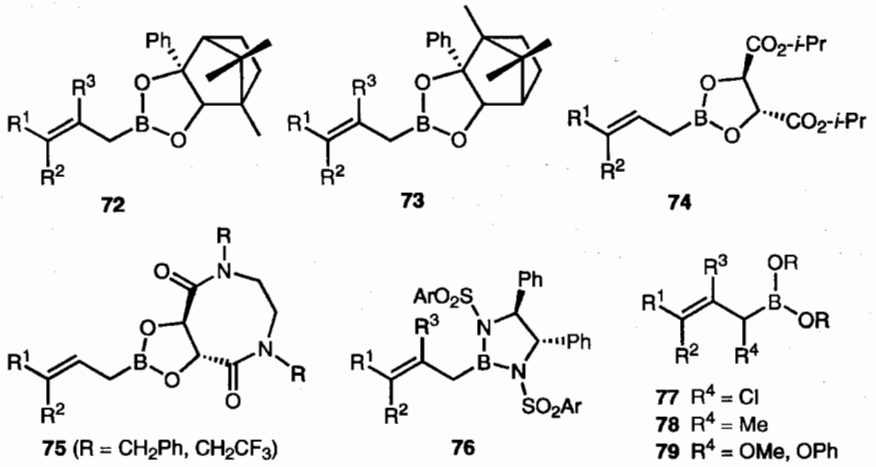


Figure 6.7 Common chiral allylboronates used in enantioselective carbonyl additions.

they did not provide very high levels of stereoinduction in their reactions with aldehydes, these reagents inspired more work by several other groups, and these efforts led to more efficient systems. For example, the class of tartrate-derived allenyl-, propargyl- and substituted allylboronates **74** first reported by Yamamoto [101] and Roush [102] evolved into one of the most recognizable class of reagents in organic synthesis. Although simple stereoselection with reagents **74** does not provide practical levels of enantioselectivity, the use of these reagents in double diastereoselection with chiral aldehydes has been amply demonstrated in the context of numerous total syntheses of complex natural products [2]. Originally, it was proposed that lone pair repulsions between one of the tartrate ester carbonyl and the aldehyde oxygen in T.S. **B** were responsible for the preference for T.S. A and the consequent enantiofacial selectivity (Figure 6.8). Recent theoretical calculations, however, point to an attractive n_O–$p^*_{C=O}$ interaction between the basic oxygen atom of one of the two carboxyesters and the boron-activated aldehyde carbonyl as the main factor favoring T.S. A in these stereoselective allylations [103].

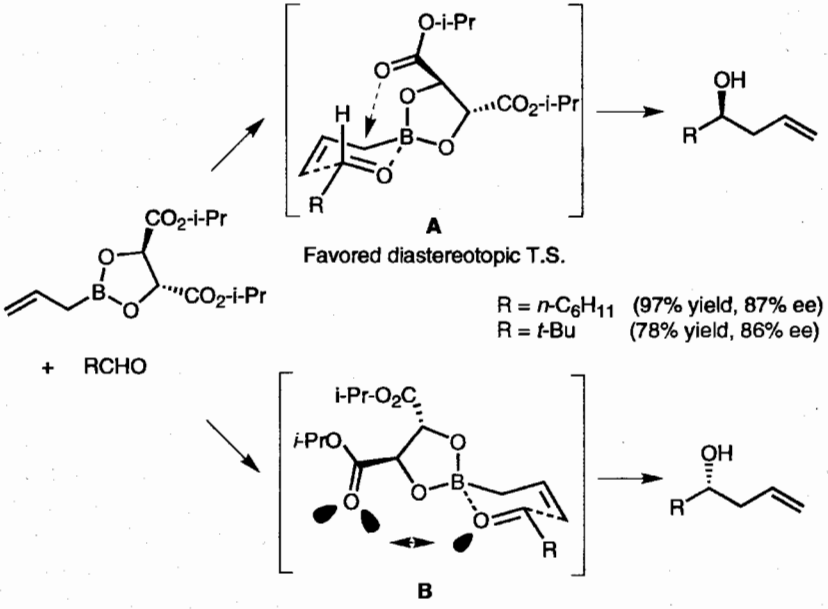


Figure 6.8 Model for absolute stereoinduction in additions of tartrate allylboronates to aldehydes.

Cyclic derivatives **75** lead to higher levels of enantioselectivity but their preparation require more effort than for the simpler reagents **74** [104, 105]. Corey and co-workers reported the bis(sulfonamide) derivatives of type **76**, which provide very high enantioselectivity (>95% ee) in the case of unsubstituted allyl and 2-substituted reagents [30]. The recent advent of the Lewis acid-catalyzed manifold (Section 6.3.1.2) opened new doors for enantioselective allylborations and motivated the reexamination of several chiral auxiliary systems. In this perspective, reagents **73**, one of the two classes

of camphordiol-substituted allylboronates developed by Hoffmann and co-workers, were revealed to be extremely enantioselective at –78 °C in the presence of $Sc(OTf)_3$ as catalyst [98, 99]. Consistently high levels of absolute stereoinduction (>95% ee) are observed with a broad range of aldehydes for the unsubstituted allyl reagent (**73a**) as well as the methallyl reagent **73b**, and both (*E*)- and (*Z*)-crotyl reagents **73c** and **74d** (Figure 6.9). Although this method requires a stoichiometric amount of chiral diol auxiliary, this diol is readily recovered after the reaction, and the exceptional levels of stereoinduction coupled with the operational simplicity of the reaction make it a valuable addition to stereoselective methodology.

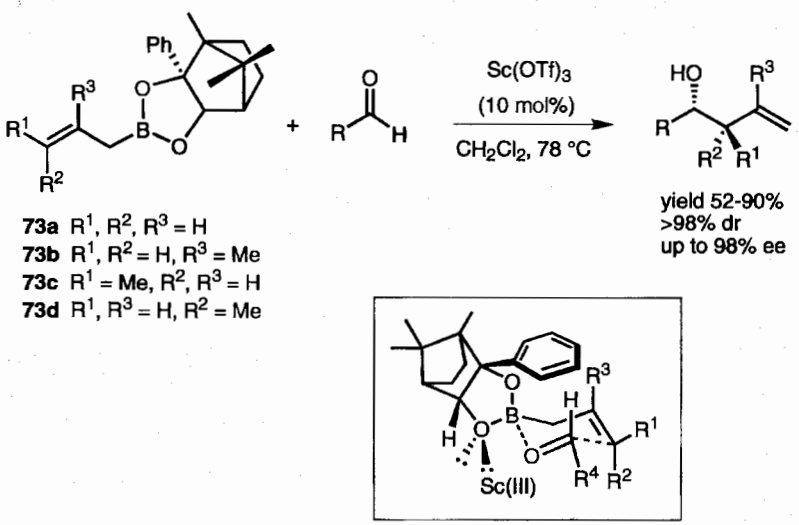


Figure 6.9 $Sc(OTf)_3$-catalyzed enantioselective addition of camphordiol allylboronates **73**.

Based on recent mechanistic studies [100], a closed bimolecular transition structure involving activation of the boronate via coordination of the scandium to one of the dioxaborolane oxygen atoms was proposed (box, Figure 6.9). A possible interpretation to explain the enantioselectivity of this allylation system originates from the accepted stereoinduction model for the non-catalyzed reaction based on a π_{phenyl}–$\pi^*_{C=O}$ attraction [62]. The Sc(III) ion is proposed to coordinate to the least hindered lone pair (*syn* to H) of the pseudo-equatorial oxygen, thereby suppressing n_O–p_B conjugation and maximizing boron–carbonyl bonding [100].

One major advantage of B-chiral reagents over C-chiral reagents is that the chiral diol or diamine unit is not involved in the bond making process and is, thus, recyclable. Although the preparation of C-chiral reagents requires a stereoinductive transformation such as the Matteson asymmetric homologation (Section 6.2.1.2), and their addition to aldehydes leads to destruction of the α-stereogenic center, these reagents have also been used extensively in the total synthesis of complex natural products [2, 6]. From the useful α-chloroallylboronates **77** [43, 68, 106], several other

C-chiral reagents can be obtained by nucleophilic substitution of the chloride. For example, the C-chiral α-alkyl [107] and α-alkoxy [108] substituted reagents **78** and **79**, developed by Hoffman and co-workers, provide excellent transfer of chirality with levels of enantiocontrol over 95% ee. These reagents provide interesting insight into the important steric and electronic factors involved in the allylboration transition state. For all of these α-chiral reagents, two competing chair-like transition structure models can be proposed in which the alpha substituent is positioned either in a pseudo-equatorial or in a pseudo-axial orientation. These two competing structures lead to opposite enantiomers of the resulting homoallylic alcohols, and their relative energy difference depends on the nature of the substituent on the α-carbon, and also on the presence of 3-substituents on the allylboronate. For example, with the α-chloro reagent **21**, the (*Z*)-chloroalkenyl homoallylic alcohol product **80** is largely predominant (>99:1) over (*E*)-configured product **81**, and it is obtained in a very high level of enantioselectivity (Figure 6.10) [43]. The predominance of stereoisomer **80** and its (*Z*)-olefin geometry can be explained in terms of a preferred transition structure **A** whereby the chloro substituent adopts a pseudo-axial orientation to minimize dipoles, and to avoid coulombic repulsions with the boronate's oxygen atoms. In transition structure **B**, unfavorable steric interactions between the pseudo-equatorial chloro substituent and the dioxaborolane substituents are unavoidable. The authors had previously shown that the DICHED auxiliary had no effect on the stereochemical outcome of the reaction [36]. Thus, the α-chloro center and not the chiral boronate unit is the main contributor to the highly efficient transfer of chirality in these allylations.

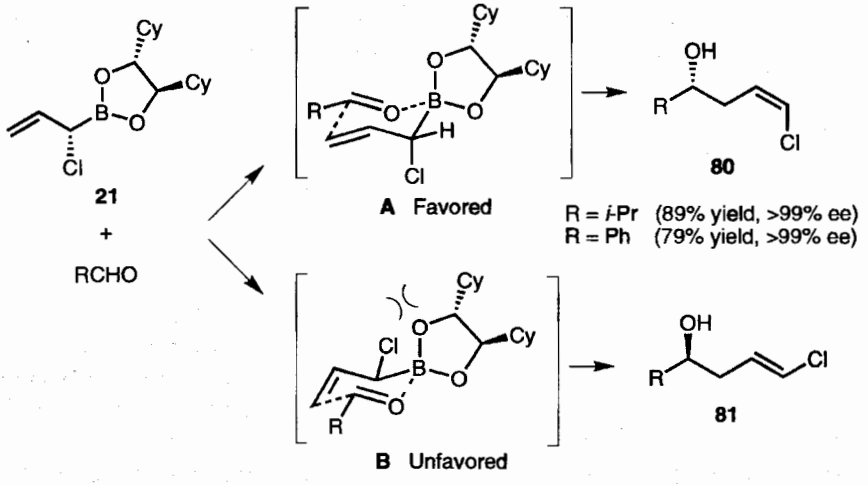
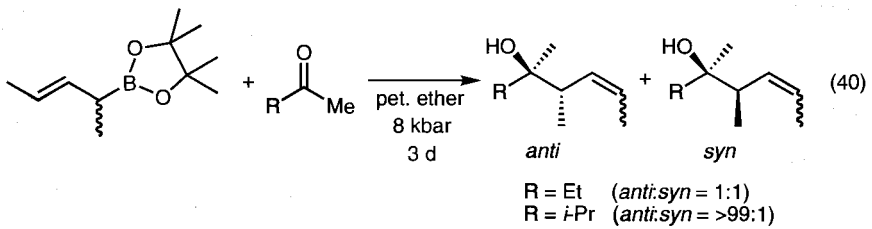


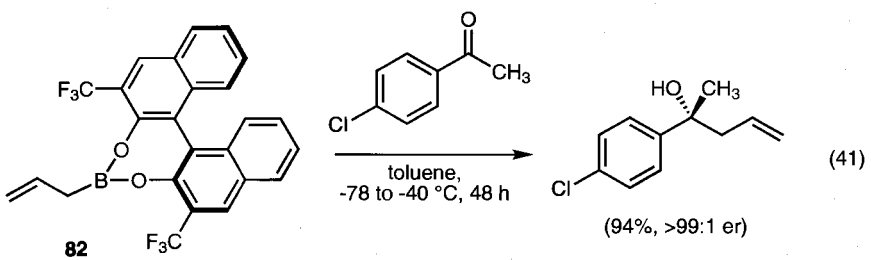
Figure 6.10 Stereoinduction model for the additions of chiral α-chloroallylboronate **21**.

6.3.2
Additions to Ketones

Although most reactions of allylboronates involve aldehydes, other electrophilic partners are also possible. As exemplified in Equation 40, ketones can also react with allylboronates, yielding tertiary homoallylic alcohols [109]. Additions with simple ketones are much slower than similar reactions with aldehydes, and the stereoselectivity in these additions is quite variable, depending on the difference in size between the two substituents on the ketone. This was also noted in a recent study of binaphthol-derived allylboronates, where high levels of enantioselection (>96% ee) were obtained in the reaction of 3,3′-$(CF_3)_2$-BINOL allylboronate **82** with several aromatic ketones (Equation 41) [110].

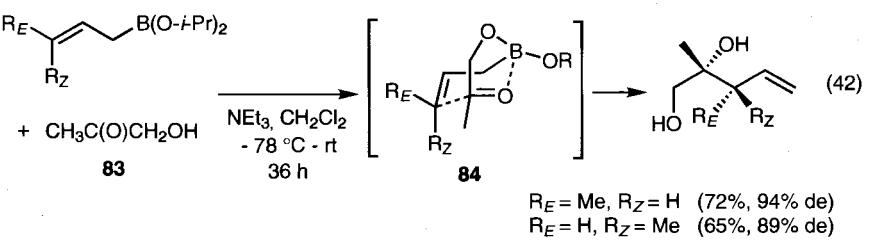


(40)



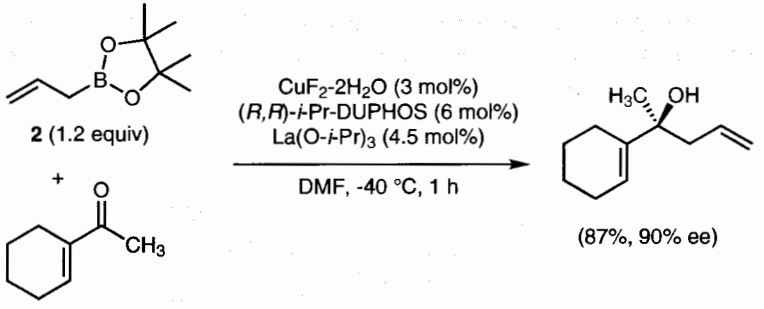
(41)

Additions of allylboronates onto ketones are greatly enhanced if an appropriate chelating group is present on the ketone (e.g., an α- or β-hydroxyl or carboxylic acid group) [111–115]. For example, Kabalka and co-workers observed that both *E* and *Z* diisopropyl crotylboronates add to α-hydroxyketone 83 within reasonable time frames to give the expected products with partial preservation of the olefin geometry (Equation 42) [116]. In the proposed transition state 84, the ketone residue bearing this α-hydroxyl group occupies the axial position due to formation of a cyclic boronic ester. Moderate levels of diastereomeric differentiation were seen in the additions of achiral allylboronates to stereogenic β-hydroxyketones [117].



(42)

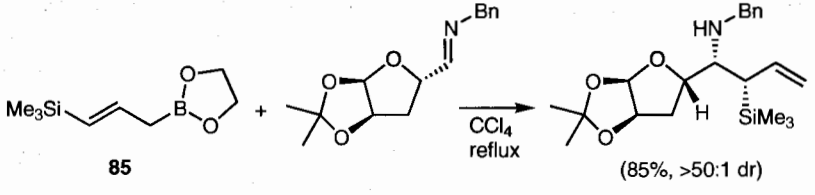
Recently, Shibasaki and co-workers reported a copper-catalyzed reaction using a chiral diphosphine ligand, DuPHOS, with an added lanthanide salt [118]. This new allylation system provides good levels of enantioselectivity in additions of the simple allylboronate **2** to either aromatic or aliphatic ketones that present a large difference of steric bulk on both sides of the carbonyl (Equation 43). Based on ^{11}B NMR experiments and on the lack of diastereoselectivity in crotylation examples, the suggested mechanism of this allylation involves transmetallation of the boron to an allylcopper species.



(43)

6.3.3
Additions to Imine Derivatives

Reactions of allylboronates with imines [119, 120] and oximes [119, **121–123**] have also been documented. These reactions are attractive because they lead to homoallylic amines as products. They are much slower than similar reactions with aldehydes and the additions are often less selective. Prediction of their stereochemical outcome is complicated by the possibilities that they may proceed via boat-like transition states, and the imine or oxime substrate might undergo *E*–*Z* isomerization under the harsh conditions of the additions. Wuts and co-workers, however, observed that (*E*)-3-trialkylsilyl-substituted reagents like **85** are particularly effective for additions to *N*-benzyl imine derivatives (Equation 44) [124]. A few examples of enantioselective additions have been reported [125, 126], one of the more successful being the addition of the 2-carboxyester allylboronate **86** to imine **87**, yielding *exo*-methylene γ-lactam **88** as a pure enantiomer (Equation 45) [127].



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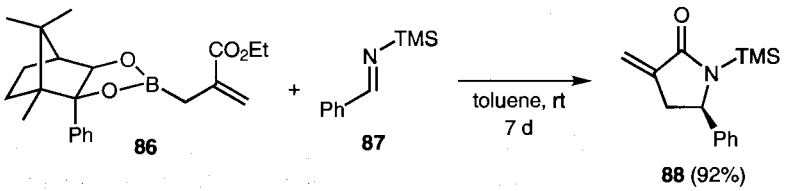
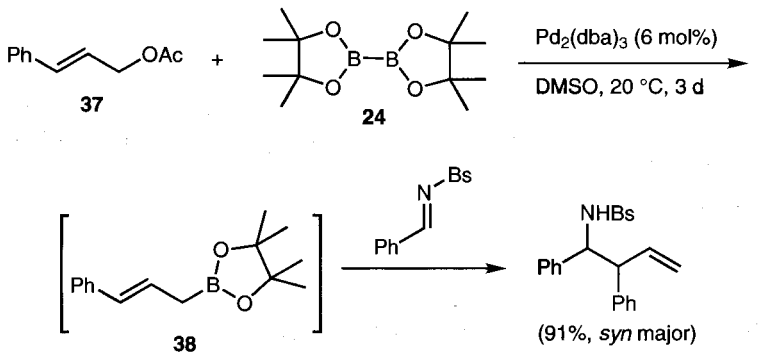


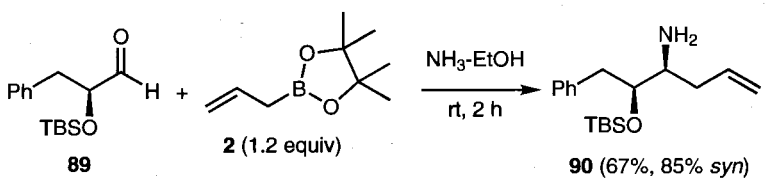
(45)

In the recent development of a one-pot borylation of allylic acetates (e.g., **37**) followed by in situ addition to sulfonyl-imines, Szabó and co-workers observed that the palladium catalyst is required for the addition of the transient allylboronate **38** to the *N*-sulfonyl imine (Equation 46) [59]. The authors proposed the intermediacy of a bis-allylpalladium species to explain this result. These additions are highly regio- and stereoselective.



(46)

Recently, Kobayashi and co-workers reported an interesting variant for the synthesis of homoallylic amines, dubbed an "ammonia fixation" reaction [128]. With this method, allylboronates are reacted with aldehydes in a solution of ethanolic ammonia. Despite the highly basic conditions, optically pure protected α-hydroxy aldehydes such as **89** can be employed without any observed racemization, and this approach was applied to the synthesis of aminosugar derivatives via aminoalcohol product **90** (Equation 47). Unfortunately, the addition of a chiral camphor-based allylboronate to benzaldehyde led only to a low enantioselectivity (34% ee). Reactions with the (*E*)- and (*Z*)-pinacol crotylboronates lead to the same diastereoselectivity seen in the corresponding reactions with aldehydes, affording the respective *anti* and *syn* products from a reaction mechanism that most likely involves the intermediacy of primary imines.



(47)

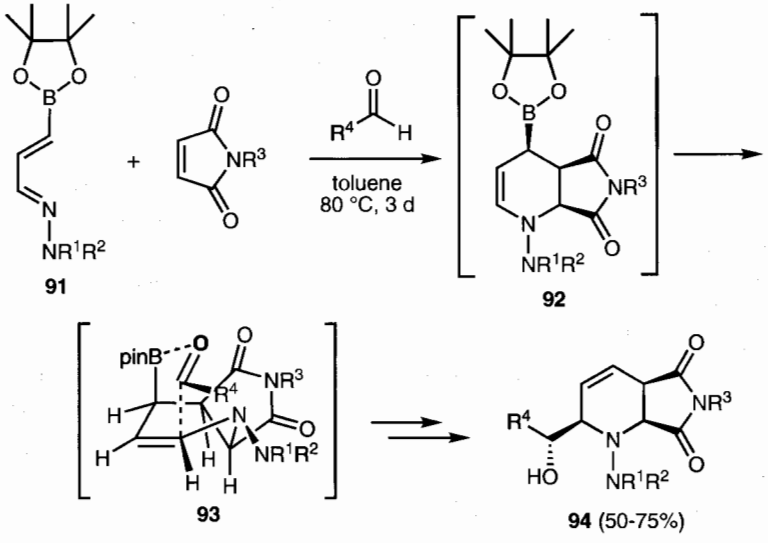
6.4
Applications of Allylboronates in Tandem Reactions with Carbonyl Compounds

Many recent advances in the synthetic applications of allylboronates have focused on the use of these reagents as key components of tandem reactions and "one-pot" sequential processes, including multicomponent processes. The following sections summarize some recent examples.

6.4.1
Allylboration as the Terminal Process

6.4.1.1 Tandem [4+2] Cycloaddition/Allylation

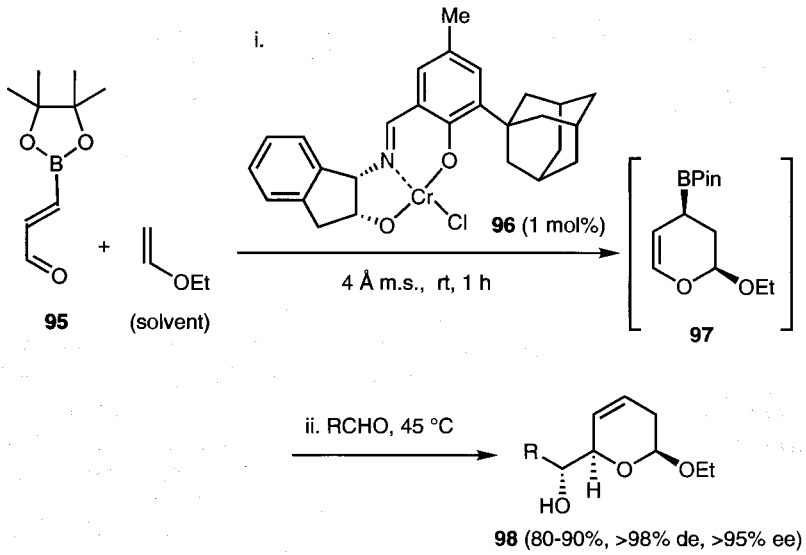
Inspired by the pioneering work of Vaultier and co-workers on the two-step carbocyclic [4+2] cycloaddition/allylboration [78] and the one-pot variant by Lallemand [79], Tailor and Hall described the first tandem aza[4+2]cycloaddition/allylboration three-component reaction [129]. Thermal reaction between hydrazonobutadienes **91**, *N*-substituted maleimides, and aldehydes provides polysubstituted α-hydroxyalkylpiperidines **94** via the allylboronate intermediate **92** and the proposed allylboration transition structure **93** (Equation 48) [130]. A variant of this process, an aza[4+2]cycloaddition/allylboration/retro-sulfinyl-ene, has been applied to the total synthesis of palustrine alkaloids [131].



91 **92** **93** **94** (50-75%) (48)

Recently, the corresponding variant for constructing α-hydroxyalkyl pyran derivatives has been described. This three-component reaction involves 3-boronoacrolein pinacolate, ethyl vinyl ether, and aldehydes as components [132, 133]. By making use of Jacobsen's chiral Cr(III) catalyst **96** in the first step (i.e., the inverse electron demand Diels–Alder cycloaddition), the overall process provides the desired products

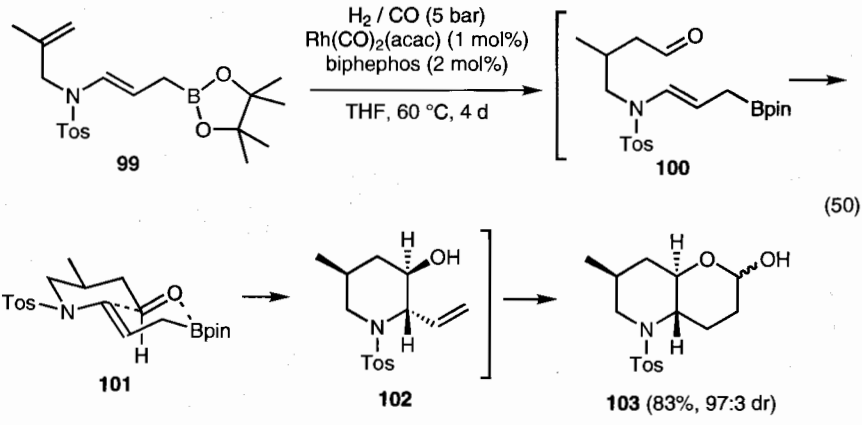
98 in high yields and over 95% diastereo- and enantioselectivity (Equation 49) [133]. This hetero-Diels–Alder step marks the first catalytic enantioselective preparation of a C-chiral allylboronate (i.e., 97). Key to this process is that the possible self-allylboration between 95 and 97 is avoided by the higher temperature required in the allylboration step. An application of this three-component reaction to the synthesis of a mosquito oviposition pheromone was also described.



(49)

6.4.1.2 Tandem Hydroformylation/Intramolecular Allylation

Hoffmann and co-workers designed an interesting domino hydroformylation/allylboration/hydroformylation reaction cascade to generate bicyclic annelated tetrahydropyrans [134] and nitrogen heterocycles [135, 136]. For example, treatment of γ-(*N*-methallyl)-amido-substituted allylboronate **99** under hydroformylation conditions first leads to aldehyde intermediate **100**, whose formation triggers the key intramolecular allylboration to give intermediate **102** (Equation 50) [136]. This intermediate then undergoes a second hydroformylation, followed by a final cyclization to give an 83% yield of the bicyclic lactol product **103** as a 1:1 mixture of anomers. The final products are obtained in this one pot-process with a very high diastereoselectivity (97:3 ratio) as a result of simple diastereocontrol in the allylboration step involving the putative transition structure **101**.

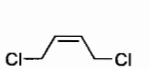
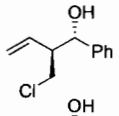
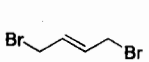
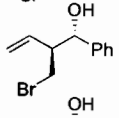
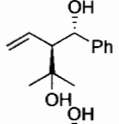
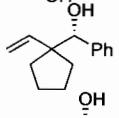
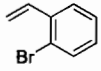
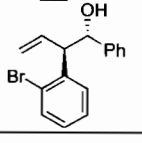


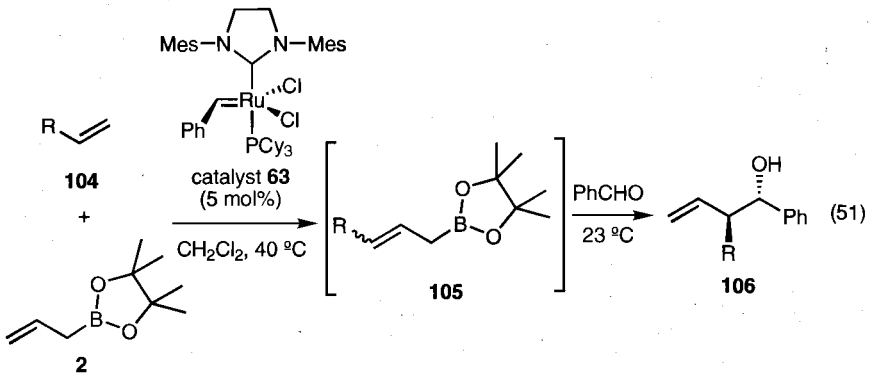
(50)

6.4.1.3 Tandem Alkene Cross-metathesis/Allylation

As described in Section 6.2.2.6, simple allylboronates can be elaborated into more substituted ones using olefin cross-metathesis (Table 6.1) [82]. In the work of Goldberg and Grubbs, treatment of pinacol allylboronate **2** with various olefin partners (**104**) in the presence of catalyst **63** smoothly leads to formation of a 3-substituted allylboronate, the cross product **105** (Equation 51). This new boronate is not isolated but rather is treated directly with benzaldehyde to give the homoallylic alcohol product **106** in good yield.

Table 6.1 Functionalized homoallylic alcohols from olefin cross metathesis.

Entry	Cross Partner 104	Product 106	Yield (%)	dr
1			73	3.8:1
2			78	4.9:1
3			58	>20:1
4			66	>20:1
5			60	>20:1

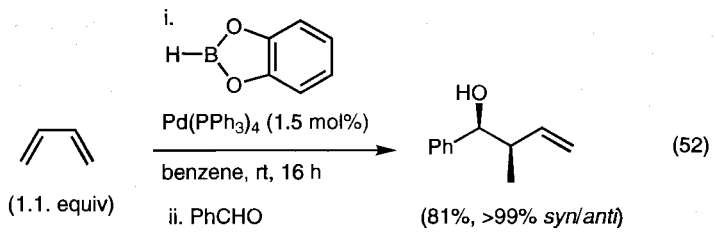


The main advantage of this sequence over others is that it is exceptionally tolerant of sensitive functional groups. Entry 3 (Table 6.1) shows an example with an unprotected alcohol, and entries 1, 2, and 5 all show examples of halogenated groups that were delivered directly from an allylboronate. These groups, which would not have survived the strongly basic conditions or the active metals used in many other preparation methods, are carried through this procedure without incident. Entry 4 is also noteworthy because it shows that quaternary carbon centers can be made with this chemistry.

A serious limitation with this preparation is that the diastereoselectivity seen in the formation of **106** is quite variable. Olefin partners **104** with large allylic substituents (e.g., entries 3–5) react to give exclusively the *anti* product **106** shown in Table 6.1. Unfortunately, olefins with smaller substituents (entries 1 and 2) show a much lower preference. Furthermore, both *E* and *Z* olefins afford the same stereoisomer of alcohol **106** (compare entries 1 and 2).

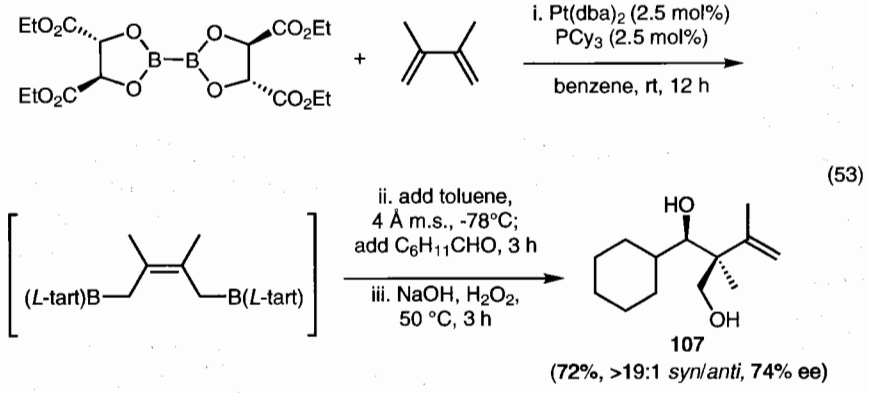
6.4.1.4 Tandem Diene Hydroboration/Allylation

The transition-metal diene hydroboration methodology described in Section 6.2.1.3 was easily incorporated as the initial step in a one-pot sequential allylation procedure. The reaction provided the expected homoallylic alcohols (Equation 52) [44].



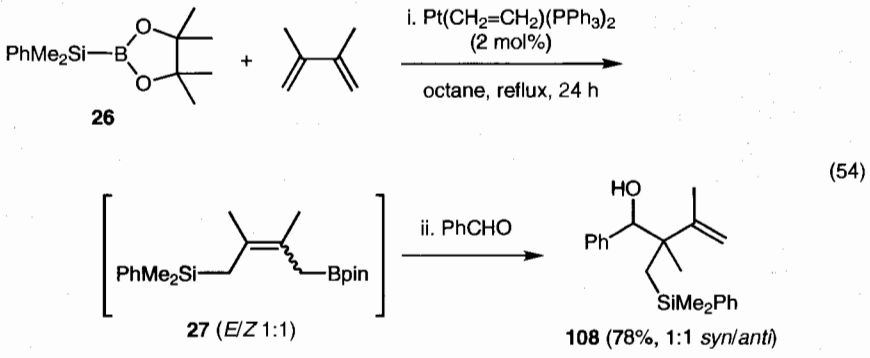
6.4.1.5 Tandem Diene Diborylation (Silaboration)/Allylboration

Morgan and Morken developed a mild one-pot procedure initiated by a platinum-catalyzed diborylation of 1,3-butadienes (Section 6.2.1.4), followed by the addition of an aldehyde to trigger a terminating allylation step that forms a quaternary carbon center in the product **107** (Equation 53) [137]. The use of a tartrate auxiliary in this process led to good levels of enantioselectivity in the final diol **107**, which was obtained after oxidation of the primary alkylboronate product. An intramolecular variant of this interesting tandem reaction was subsequently reported by the same group [138].



(53)

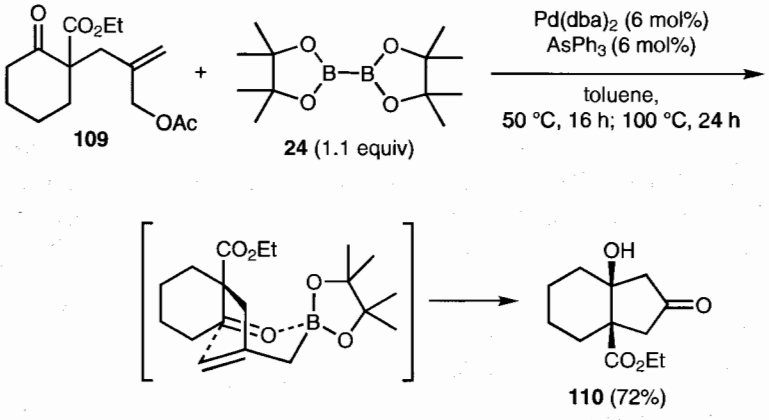
The corresponding silaboration process was developed by Ito and co-workers. Using the diene silaboration methodology described before (Section 6.2.1.4), intermediate **27** was obtained as a **1:1** mixture of isomers (Equation 54) [48]. Benzaldehyde was then added to the reaction mixture and the corresponding allylation product **108** was obtained in a good yield, albeit as a 1:1 diastereomeric mixture. This poor diastereoselectivity was expected due to the isomerization of **27** under the reaction conditions. Efforts to trap **27** prior to isomerization by conducting the silaboration in the presence of the aldehyde led to the surprising discovery of a highly diastereoselective platinum-catalyzed allylsilation process instead of the expected allylboration. Conversely, product **108** can be obtained diastereomerically pure in a two-step sequence using (*Z*)-**27** accessed through the improved nickel-catalyzed procedure described above [49].



(54)

6.4.1.6 Tandem Allylic Borylation/Intramolecular Allylation

Miyaura and co-workers have developed a one-pot borylation/allylation tandem process based on the borylation of various ketone-containing allylic acetates [139]. The intramolecular allylboration step was very slow in DMSO, which is the usual solvent for these borylations of allylic acetates (Section 6.2.1.6). Alternatively, a non-coordinating solvent like toluene was more suitable for the overall process, provided an arsine or phosphine ligand is added to stabilize the active Pd(0) species during the borylation. With cyclic ketones such as **109** the intramolecular allylation provided cis-fused bicyclic products (**110**), in agreement with the involvement of the usual chair-like transition state (Equation 55). An intermolecular tandem borylation/allylation was also reported [59].

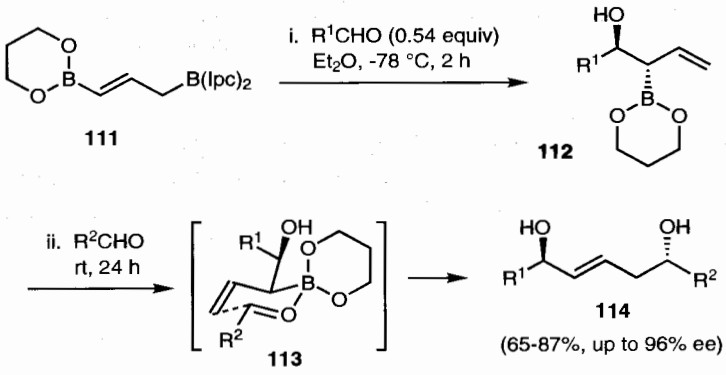


(55)

6.4.2 Allylboration as the Initiating Process

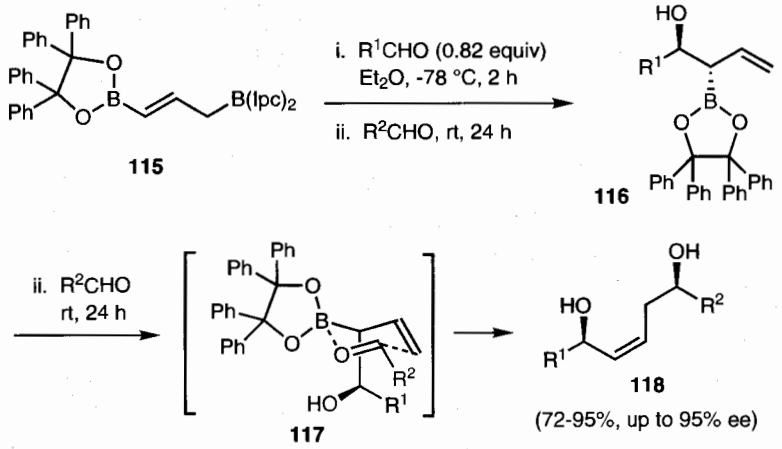
6.4.2.1 Tandem Allylation/Allylation

Inspired by the description of the 3-boronyl allylborane reagent **111** by Brown and Narla [140], Flamme and Roush designed a tandem double allylation strategy that was optimized for the synthesis of 1,5-diol products from two different aldehyde substrates [141]. Specifically, reagent **111** undergoes allylation with a limiting amount of a first aldehyde, R^1CHO, and the resulting α-chiral allylboronate **112** can then add onto a second added aldehyde (R^2CHO) (Equation 56). In line with the seminal studies of Brown and co-workers with diisopinocamphenylallylboranes, the first allylation is highly enantioselective and the resulting stereochemistry in **112** controls the fate of the second allylation. Thus, from intermediate **112**, transition structure **113**, featuring a pseudo-equatorial α-substituent, explains the stereocontrolled formation of diol **114**. Notably, the lower reactivity of **112** compared to **111**, as well as a tight control of reagent stoichiometry, minimized formation of the double allylation product of the first aldehyde (R^1CHO).



(56)

With reagent **115**, however, the corresponding allylboronate intermediate **116** is thought to favor transition structure **117** in which the α-substituent is in a pseudo-axial orientation to escape steric interactions with the bulky tetraphenyl dioxaborolane (Equation 57). This way, a *Z*-configured allylic alcohol unit of opposite stereochemistry is obtained in product **118**. Such steric control had been demonstrated before by the work of Hoffman and co-workers on α-chiral allylboronates (Section 6.3.1.3). The usefulness of this powerful tandem allylation/allylation strategy was demonstrated with several examples of both types of 1,5-diols, **114** and **118**.

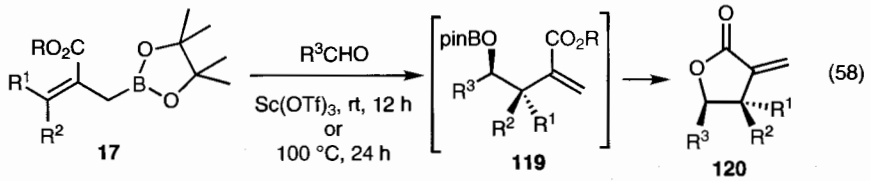


(57)

6.4.2.2 Tandem Allylation/Lactonization

Kennedy and Hall have reported a one-pot allylboration/lactonization using the tetrasubstituted 2-alkoxycarbonyl allylboronates **17** (Section 6.2.1.2) [39]. These allylboronates react with aldehydes, thermally and under Lewis acid catalysis, to first provide the hydroxy-ester intermediate **119** (Equation 58). This initial product cyclizes under the reaction conditions by lactonization to afford α-exomethylene γ-lactones **120**. This facile cyclization is probably a manifestation of the *gem*-dialkyl effect. In-

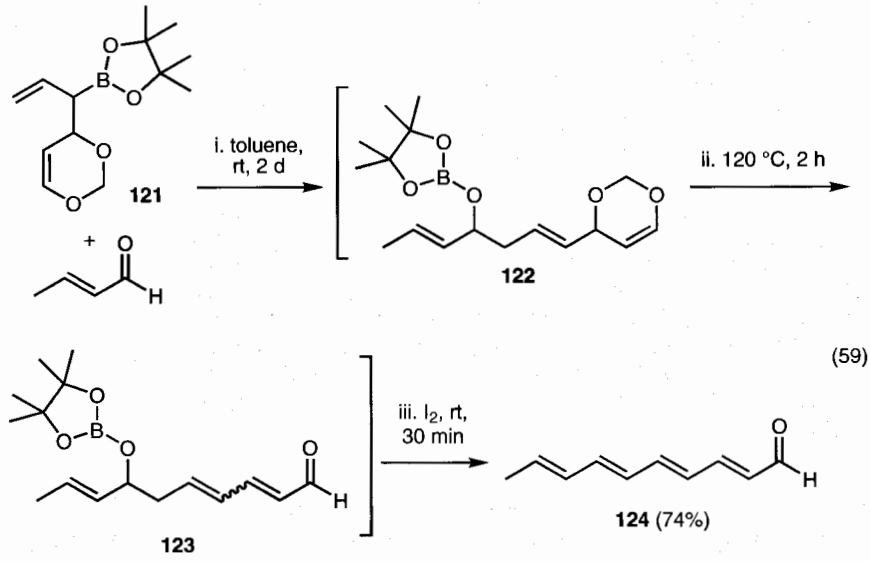
deed, only with hindered carboxyesters or 3-monosubstituted allylboronates did the lactonization not occur under the conditions of the allylboration. In such cases, treatment with mild acid provided the desired lactones. The resulting lactones could subsequently be transformed into useful synthetic intermediates [97].



(58)

6.4.2.3 Tandem Allylation/Dioxene Thermolysis

The new α-substituted allylboronate reagent **121** was developed by Hoffmann and coworkers to effect an extended homologation of aldehydes into 1,2,6-alkatrienals (Equation 59) [142]. With some unsaturated aldehydes, this method can be performed as a one-pot allylation/dioxene thermolysis/dehydration sequence. For example, reagent **121** was added to crotonaldehyde to give dioxene intermediate **122**. Upon warming to 120 °C, **122** underwent a formal retro[4+2] cycloaddition to give **123** as a mixture of geometrical isomers. The addition of iodine promotes *Z*/*E* isomerization, and the presence of adventitious HI is proposed to induce elimination of the hydroxytrienal to afford the corresponding tetraenal product **124**. For other aldehydes (both aromatic and aliphatic) dehydration must be performed as a distinct operation after the tandem allylation/thermolysis reaction in order to obtain reasonable yields.



(59)

6.5 Conclusion

The stability of allylboronates and the high level of diastereoselectivity in their additions to carbonyl compounds and imines represent very attractive attributes in organic synthesis. The examples in this chapter clearly show that recent advances in the preparation of allylboronates will help in furthering their applications. The development of efficient catalytic enantioselective allylboration methods and the invention of more powerful and more elaborate tandem reaction processes constitute two emerging areas for further development.

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7
Nucleophilic Addition Reactions of Aryl and Alkenylboronic Acids and Their Derivatives to Imines and Iminium Ions

Robert A. Batey

7.1
Introduction

The addition of carbon-centered nucleophiles to C=N bonds is one of the most powerful strategies for the formation of amines (Figure 7.1). Such approaches are direct and versatile, since a wide range of precursors are available for both the nucleophilic and electrophilic components. Carbon-centered nucleophiles employed include enols, metal enolates, enamines, alkynes, cyanide ion, isonitriles, electron-rich aromatics/heteroaromatics, and organometallic or organometalloid reagents. The substrate scope for the electrophilic C=N component includes imines, iminium ions, oximes, hydrazones, phosphonyl imines, sulfonyl imines and N-acyliminium ions. The successful implementation of this approach requires the correct partnering of the electrophilic and nucleophilic components under suitable reaction conditions. Protonated imines or iminium ions are significantly more reactive than the corresponding uncharged imines, and undergo reactions with weaker nucleophiles [1]. Undoubtedly, the most well known example of this strategy is the reaction of enols, enolates and enamines with iminium ions in the venerable Mannich reaction [2, 3].

From the class of organometallic and organometalloid nucleophiles, addition reactions are known for both hard and soft metals/metalloids [4]. There are numerous examples of stereoselective addition reactions, and considerable substrate scope is possible, with organo Mg, Li, Cu and Zn reagents representing the most commonly encountered organometallic reagents. Only relatively recently have organoboronic acids or their equivalents (e.g. organoboronates, organotrifluoroborate salts) been successfully applied in addition reactions to C=N compounds. While these organoboron derivatives are less reactive than the aforementioned organometallic reagents, there are significant advantages in their use, due to their relative stability toward air and moisture, their functional group tolerance and ease of synthesis (Chapter 1) [5]. Moreover, there are several synthetic methods for the synthesis of boronic acids, many of which are now commercially available.

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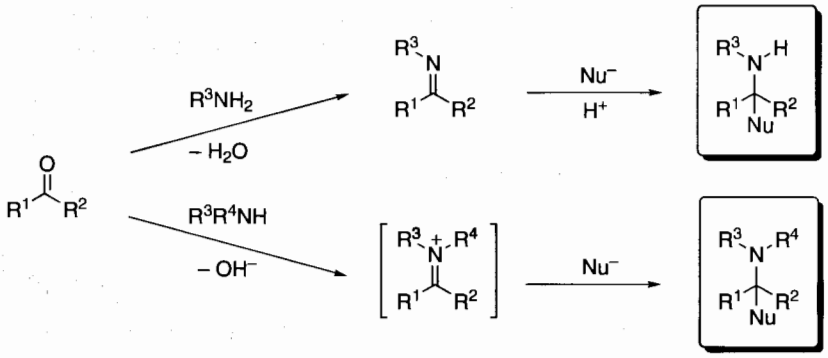


Figure 7.1 Nucleophilic addition reactions to imines and iminium ions.

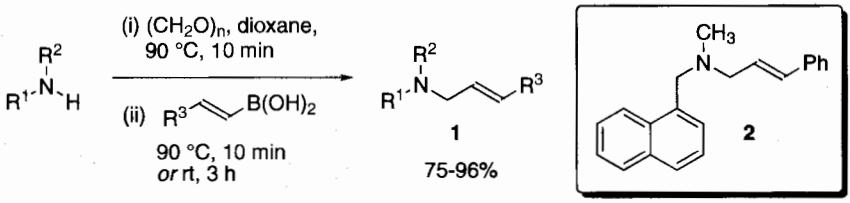
This chapter will discuss the utility of alkenyl and arylboronic acids and their derivatives in addition reactions with C=N functionality. Since there have been no major reviews of this area [6], a detailed overview of the field will be given, covering the period 1993 to early 2004.

The following areas will not be discussed: (i) organoborane additions, (ii) additions of alkyl or allyl based nucleophiles. Earlier examples of organoborane additions to C=N compounds are known, but these reactions lack generality and also suffer from the much lower stability of organoboranes [7]. A related reaction, which continues to be the subject of numerous investigations, is free-radical addition to imines using Et_3B/O_2 as an initiator [8]. Another significant class of reactions that will not be covered here are the additions of allylboronates to imines and oximes [9–15]. Notable recent advances in this area include: (i) Pd-catalyzed coupling of allyl acetates with aldehyde and imine electrophiles in the presence of bis(pinacolato)diboron [16], (ii) three-component coupling of ammonia, aldehydes and pinacol allylboronate [17], and (iii) Lewis acid promoted additions of allyl- and crotyltrifluoroborate salts to sulfonylimines [18], sulfinylimines [18] and iminium ions [19]. Various other miscellaneous reactions that will not be discussed include the addition of sodium trialkylalkynylborates to Eschenmoser's salt ($Me_2N^+=CH_2\ I^-$) [20], and $BF_3 \cdot OEt_2$ promoted additions of anions such as alkynyllithium to imines [21] or alkyl/arylcopper reagents to pyridinium salts [22]. In the latter case, Yamamoto has speculated that his $RCu \cdot BF_3$ system may involve the formation of alkyltrifluoroborate species [23].

7.2
Petasis Borono-Mannich Reaction: Iminium Ions Lacking Neighboring Heteroatom Functionality

7.2.1
Discovery of the Reaction using Paraformaldehyde

The first example of an addition reaction of an C(sp^2)–B based organoboronic acid to an iminium ion was reported by Petasis and Akritopoulou in 1993 [24]. They demonstrated the addition of (*E*)-alkenylboronic acids to preformed iminium ions derived from secondary amines and formaldehyde, to generate allylic amines **1** (Scheme 7.1). Typically, a two-stage process was employed for the formation of **1**. Initially, a secondary amine (including, dialkyl, acyclic and cyclic examples) was heated with paraformaldehyde in dioxane or toluene solvent at 90 °C for 10 min. An (*E*)-alkenylboronic acid was then added, and the solution either stirred at 90 °C for 10 min, or at room temperature for 3 h. The allylic amine product **1** was then isolated through a standard aqueous work-up (sequential treatment with aqueous HCl and NaOH). The synthetic utility of this chemistry was demonstrated in this first report by a synthesis of the oral antifungal agent naftifine (**2**).



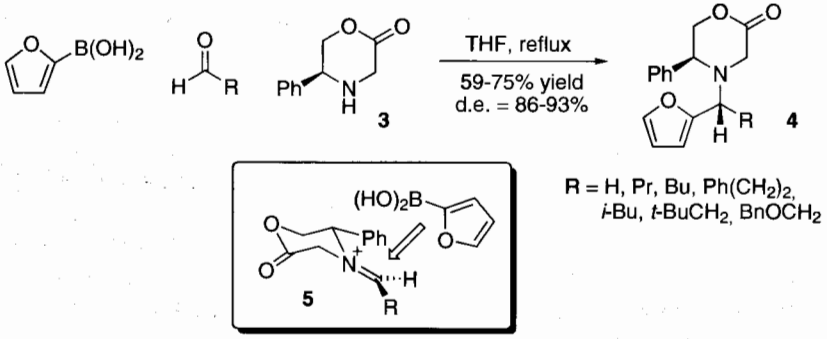
Scheme 7.1 Discovery of the Petasis borono–Mannich reaction using paraformaldehyde, amines and alkenylboronic acids.

Subsequent to this, there have been numerous reports of the use of this reaction using alkenyl, alkynyl and arylboronic acids or esters in reactions with a range of amines and aldehydes. This reaction has been variously named the "boronic Acid Mannich", "boronic Mannich", "boro-Mannich", "Petasis boronic acid-Mannich", "Petasis borono-Mannich", and "Petasis" reaction. The more inclusive term of "Petasis borono-Mannich" reaction will be used throughout this chapter.

7.2.2
Reactions of Iminium Ions Derived from Simple Aldehydes

Harwood and co-workers have reported the reaction of **3** and 2-furylboronic acid with aliphatic aldehydes (Scheme 7.2) [25, 26]. Adducts **4** were obtained in good yields and high diastereoselectivities, and are valuable intermediates for the formation of α-amino acids. This is an interesting reaction, since not only was it the first example of a stereoselective Petasis borono-Mannich reaction, but it also represents a rare example of the successful use of simple aliphatic aldehydes. Its success may be due to the

high reactivity of 2-furylboronic acid, as no other boronic acids were reported in the reaction. α-Branched aldehydes (e.g., R = *i*-Pr and Chx) gave very poor yields of adducts. The diastereoselectivity is believed to arise through attack of 2-furylboronic acid from the less hindered face of the iminium ion **5**, the geometry of which is controlled by minimizing $A^{1,3}$-strain between the Ph and R substituents in a chair-like conformation.



Scheme 7.2 Petasis borono–Mannich reaction of 2-furylboronic acid, aldehydes and secondary amines.

7.3
Practicality, Scope and Reaction Mechanism

7.3.1
Synthetic Benefits of the Petasis Borono-Mannich Reaction

The Petasis borono-Mannich reaction offers numerous practical advantages. The reaction conditions are experimentally straightforward, and it is not necessary to use anhydrous or deoxygenated solvents. No metal catalysts or Lewis/Brønsted acids/bases are required. Work-up is straightforward, and the only by-product, boric acid, is innocuous. The reaction is remarkably tolerant of functional groups, including hydroxyl, carboxylic acid and amine functionality, and is also suitable for use in solid-supported variants (Section 7.5). In principle, the regiochemistry of addition of an aromatic nucleophile can be controlled by the position of the boronic acid functionality. In addition, stereocontrolled additions can be accomplished by the use of either iminium ions or boronic acids that contain neighboring stereocenters (Section 7.4).

An inherent advantage of the Petasis borono-Mannich reaction is the ability to conduct reactions in a three-component fashion, since the imine or iminium ion intermediates can be formed in situ from the condensation of either primary or secondary amines with the corresponding aldehydes or ketones. The operational advantages of such a three-component coupling approach, combined with the practical benefits outlined above, render the Petasis borono-Mannich reaction particularly desirable for parallel synthesis applications and in the generation of combinatorial libraries. In-

deed, the Petasis reaction joins a relatively short list of other general multi-component reactions, such as the Ugi, Biginelli, Strecker and Povarov reactions [27–29].

7.3.2 Mechanistic Observations

There are no reports of detailed mechanistic studies on the Petasis borono-Mannich reaction. Nevertheless, some experimental observations have been made that provide a basic understanding of the reaction. These observations also provide some useful guidelines as to the types of substrates that are suitable for participation in the Petasis borono-Mannich reaction.

Petasis' original observations in the three-component coupling of secondary amines, (*E*)-alkenylboronic acids and formaldehyde seemed to argue against the intermediacy of iminium ions [24]. Thus, the pre-formed iminium ion, Eschenmoser's salt ($Me_2N^+=CH_2\ I^-$) was reported to not "readily add" to alkenylboronic acids. However, alkenylboronic acids were shown to undergo addition reactions with diaminomethanes. These observations are consistent with a mechanism in which both a reactive iminium ion intermediate **6** *and* an activated tetracoordinate boronate anion **7** are necessary for addition to occur (Figure 7.2). For the direct reaction of a boronic acid with Eschenmoser's salt, addition may be prevented, since the weakly Lewis basic iodide counter-ion does not allow the formation of a nucleophilic tetracoordinate boronate anion. The exact nature of the addition step between **6** and **7** is unknown, but the fact that the reaction is only known for alkenyl, aryl and alkynylboronic acids (i.e. systems containing a π-bond directly attached to the boron atom), may suggest an addition–elimination type mechanism that results in overall ipso substitution. An alternative direct displacement step cannot be ruled out, but would have to account for the retention of configuration observed in reactions of geometrically defined alkenylboronates. Another suggested mechanistic possibility is direct reaction via complex **8**, although such a concerted process would appear to be unfavorable on stereoelectronic grounds.

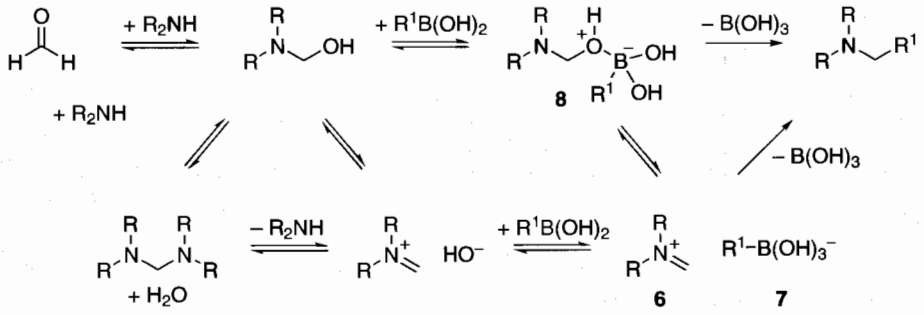


Figure 7.2 General mechanism for the condensation of boronic acids with secondary amines and formaldehyde via the addition of an activated tetracoordinate anionic boron species to iminium ions.

7.3.3
Substrate Scope and the Effect of Neighboring Heteroatoms

Most examples of the Petasis borono-Mannich reaction utilize non-enolizable aldehydes bearing α- or, less commonly, β-heteroatom functionality (Section 7.4). In these cases it has been proposed that the neighboring heteroatom group facilitates addition via a tetracoordinate borate species such as **9**, **10** or **11** (Figure 7.3). The anionic borate is much more nucleophilic than tricoordinate boronic acids or esters, and the templating or tethering effect locates the nucleophilic alkenyl or aryl groups in a position where they can be transferred to the iminium ion in an intramolecular manner. Thus, while salicylaldehyde has been widely used, arylaldehydes that do not possess neighboring ortho-hydroxyl functionality typically do not participate in the Petasis borono-Mannich reaction [30]. An exception is the result of Harwood with highly reactive 2-furylboronic acids, vide supra (Scheme 7.2) [25, 26]. The ortho-hydroxyl functionality of salicylaldehyde is thus implicated as the key activating group in the reaction (Figure 7.3) [31]. Similar activation has been suggested for the reactions of α-hydroxy iminium ions (Section 7.4.2 and Equation 5) [32]. For reactions with glyoxylic acid or related substrates, the intermediate iminium ions are highly electron deficient due to the presence of the carboxylate group, which probably also serves as an activating group (Figure 7.3) [33]. Some support for this hypothesis is provided by the NMR observations of Hansen and co-workers, which show that, on mixing phenylboronic acid with glyoxylic acid, an upfield shift in the ^{11}B NMR occurs, from that of δ 33.5 ppm for $PhB(OH)_2$ to δ 14.2 ppm – consistent with the formation of a tetracoordinate boronate species [33].

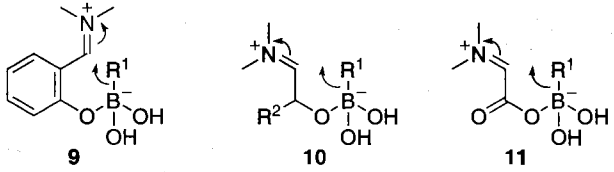
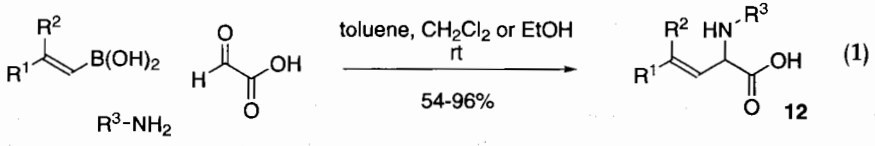


Figure 7.3 Putative coordinated intermediates involved in Petasis borono–Mannich reactions of aldehydes possessing neighboring heteroatoms.

7.4
Petasis Borono-Mannich Reaction: Iminium Ions Possessing Neighboring Heteroatom Functionality

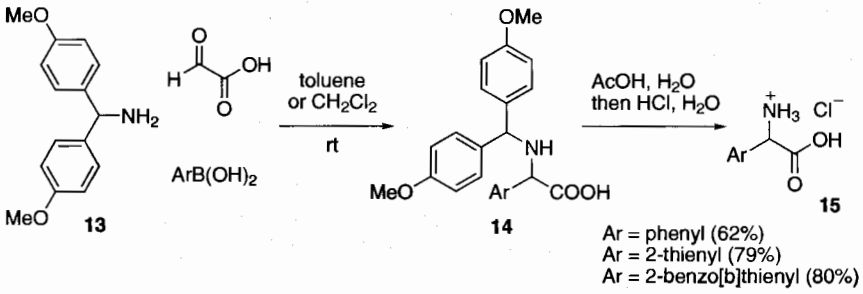
7.4.1
Reactions of Glyoxylic Acid-derived Iminium Ions

Glyoxylic acid monohydrate ($CHOCOOH \cdot H_2O$) is the most commonly used aldehyde component in the Petasis borono-Mannich reaction. For example, Petasis and Zavialov showed that alkenylboronic acids undergo additions with glyoxylic acid monohydrate and primary amines to give the corresponding α-amino acid derivatives **12** (Equation 1) [34]. The reaction proceeds via a directed or tethered species of type **11** (Figure 7.3). Examples of primary amines used in this reaction include anilines, benzylamine, 2-aminoethanol, aminodiarylmethanes and tritylamine. The reaction tolerates bromo substituents at the β-position of the alkenylboronic esters, and can also be achieved using secondary amines such as morpholine, as well as using pyruvic acid ($CH_3COCOOH$) as the carbonyl component.



(1)

Aryl and heteroarylboronic acids react similarly in additions with glyoxylic acid monohydrate and primary amines [35]. The use of amino-bis(4-methoxyphenyl)-methane (**13**) as the amine component generates adducts **14** that are readily deprotected under acidic conditions to the free amino acid salts **15** (Scheme 7.3). Jiang and co-workers have shown that 3-indolylboronic acid derivatives react with glyoxylic acid and aminodiphenylmethane [36]. In a model study for the synthesis of the alkaloid conessine, Jiang and co-workers also employed the Petasis borono-Mannich reaction with propargylic amines, glyoxylic acid and 3,4-dihydronaphthalene-2-boronic acid [37].

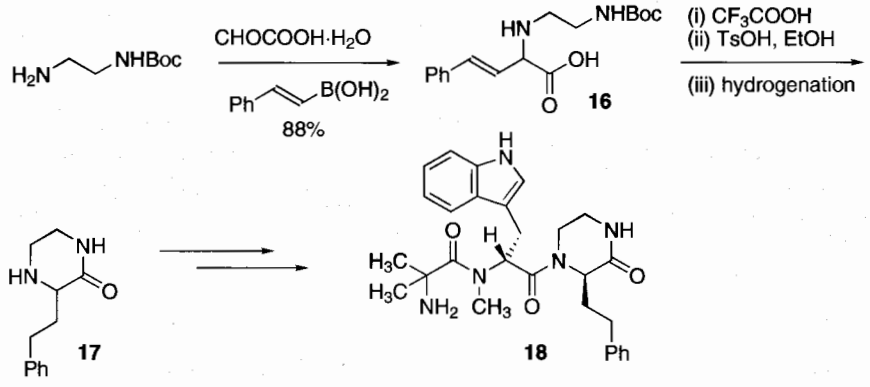


Scheme 7.3 Synthesis of α-amino acids using the Petasis borono–Mannich reaction.

Boronic esters will also react under appropriate circumstances. Petasis used bis(isopropyl) (2*E*)-bromoethenylboronic ester in a reaction with glyoxylic acid and aminodiphenylmethane [34]. Scobie and co-workers have reported the coupling of pinacolyl aryl and alkenylboronic esters with secondary amines [38]. The reaction gave good yields with alkenylboronic esters (70–82%), but worked poorly with arylboronic esters (0–12%). In contrast to the above results, the reaction did not proceed with primary amines under the same conditions.

Microwave acceleration of reactions is a valuable tool for organic synthesis [39], and various specialized instruments are now commercially available. Tye and co-workers have reported the microwave-assisted Petasis borono-Mannich reaction of arylboronic acids and primary or secondary amines with either glyoxylic acid or salicylaldehyde [40]. Optimized reaction conditions employed dichloromethane as solvent, and microwave assisted heating at 120 °C for 10 min. Products were obtained in generally modest yields (10–83%), in part due to incomplete reaction conversion under the reported conditions.

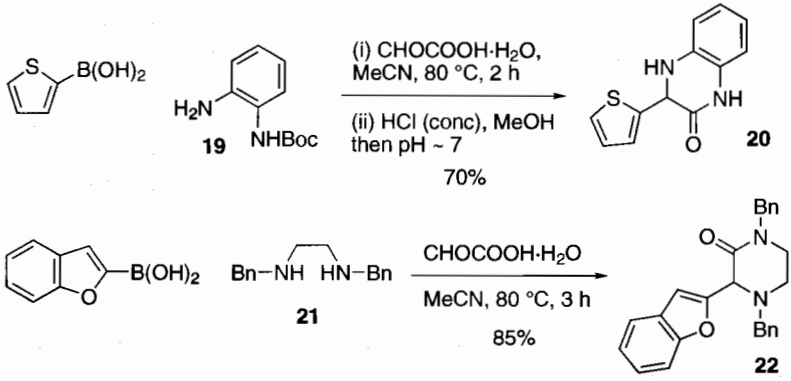
The coupling of 1,2-diamines, glyoxylic acid and organoboronic acids, followed by lactamization has been used to generate piperazinones [41, 42] and benzopiperazinones [41]. Hansen and co-workers used the Petasis borono-Mannich to create the α-amino acid **16**, which was then Boc-deprotected, cyclized and hydrogenated to give the 2-piperazinone **17** (Scheme 7.4) [42]. Although further details were not given, this compound was then elaborated into **18**, which acts as a conformationally restrained analog of an orally active growth hormone secretagogue molecule. Sequential combination of a Petasis borono-Mannich reaction with a cyclization reaction represents a valuable approach to heterocycle formation.



Scheme 7.4 Synthesis of 2-piperazinones using the Petasis borono–Mannich reaction.

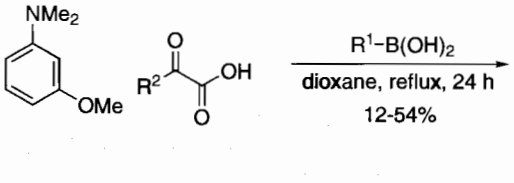
A similar approach has been outlined by Petasis and Patel for the formation of piperazinones and benzopiperazinones, using either stepwise or "one-pot" protocols (Scheme 7.5) [41]. A sequential protocol was used for reactions of mono-Boc protected ethylenediamines, 1,2-cyclohexanediamines or 1,2-phenylenediamines **19**. Standard conditions were used for the Petasis borono-Mannich reaction, followed by Boc

deprotection and in situ cyclization. For reactions of 1,2-cyclohexanediamines, diastereoselectivities were modest (40–73% de). Interestingly, the 2-thienyl product **20** served as a useful precursor for a further Petasis borono-Mannich reaction. A "one-pot" protocol was used for the reactions of symmetrical *N,N'*-dialkylethylenediamines **21** or 1,2-cyclohexanediamines, as exemplified by the formation of **22** (Scheme 7.5).



Scheme 7.5 Synthesis of benzopiperazinones and 2-piperazinones using the Petasis borono–Mannich reaction.

The Petasis borono-Mannich reaction requires the use of either mono- or disubstituted amines. Naskar and co-workers have reported a related reaction using the tertiary amine 3-alkoxy-*N,N*-dimethylaniline and glyoxylic acid to give **23** (Equation 2) [43]. This reaction results in the formation of two C–C bonds, rather than C–C and C–N bond formation as occurs in the standard Petasis borono-Mannich reaction. The reaction is unlikely to be general, requiring the use of highly electron-rich aromatic compounds. Both glyoxylic acid and α-ketoacid derivatives undergo the reaction with aryl, heteroaryl and alkenylboronic acids. Naskar has also reported a similar reaction of 1,3,5-trioxygenated benzenes [44].

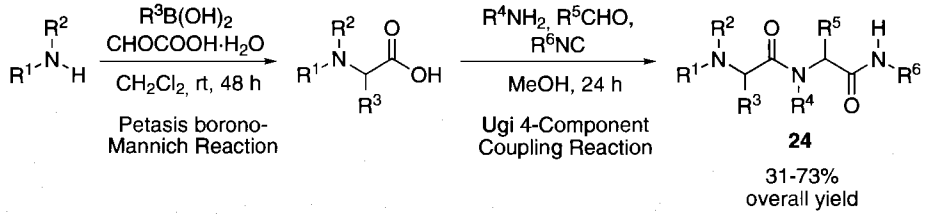


(2)

R^1 = aryl, heteroaryl, alkenyl
R^2 = H, Me, Et, Ph, Bn

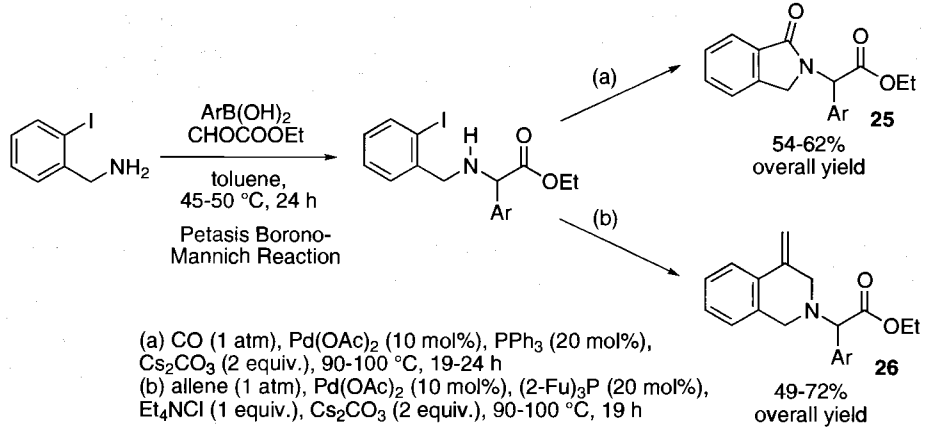
Portlock and co-workers have demonstrated the sequential use of a Petasis borono-Mannich reaction and an Ugi 4-component coupling reaction for the generation of dipeptide amides **24** (Scheme 7.6) [45]. Exchange of the solvent from dichloromethane to MeOH was required between the Petasis borono-Mannich and Ugi reac-

tions. Products were obtained in modest yields (31–54%), as racemic and diastereomeric mixtures, when using equimolar amounts of each of the components. In contrast, a higher yield (73%) was obtained when using the isonitrile component as the limiting reagent (0.8 equiv). Although only a few examples were reported, this sequential reaction combination has the potential to be applied to the formation of large combinatorial libraries, with six points of diversity in the products.



Scheme 7.6 Sequential use of Petasis borono–Mannich and Ugi 4-component coupling reactions for the generation of dipeptide amides.

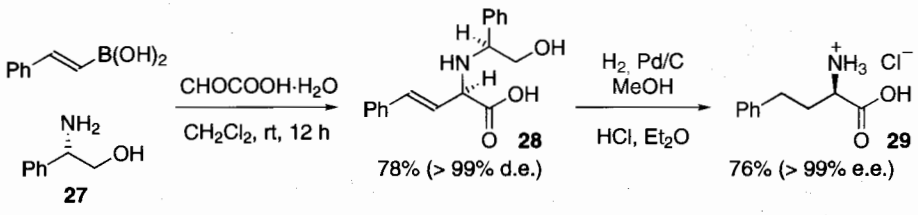
Grigg and co-workers have used a sequential, "one-pot" Petasis borono-Mannich reaction with either Pd(0)-catalyzed carbonylative amination cyclization or Pd(0)-catalyzed allenylation/amination cyclization (Scheme 7.7) [46]. The overall approach results in the formation of α-amino acid derivatives of isoindolone **25** and 4-methylene-3,4-dihydroisoquinoline **26**. While this is the only reported example of a combination of a Petasis borono-Mannich reaction with a Pd(0)-catalyzed reaction, the possibility of using other Pd(0) or transition metal catalyzed reactions is a very attractive strategy for the synthesis of complex molecules or combinatorial libraries.



Scheme 7.7 Sequential use of Petasis borono–Mannich and Pd-catalyzed coupling reactions for the generation of nitrogen heterocycles.

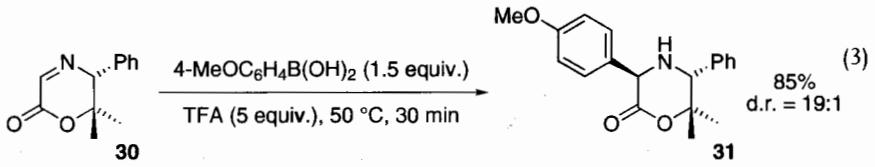
7.4.1.1 Diastereoselective Addition Reactions to Iminium Ions Derived from Chiral Amines and Glyoxylic Acid

Diastereoselective Petasis borono-Mannich reactions are possible using chiral amines. Addition of arylboronic acids to α-methylbenzylamine and glyoxylic acid, however, results in relatively poor stereoselectivities [35]. Slightly improved levels of diastereoselectivity were observed in the reactions of alkenylboronic acids under similar conditions [34]. The coupling of 3-indolylboronic acid derivatives with glyoxylic acid and α-methylbenzylamine have been reported to proceed in good yields, with the adducts being isolated in high diastereoselectivities upon recrystallization [36]. Petasis has shown that significantly improved selectivities can be achieved using phenylglycinol **27** (Scheme 7.8) [34]. The resulting adducts (**28**) can be deprotected to yield enantiopure α-amino acids **29**.



Scheme 7.8 Enantioselective synthesis of α-amino acids using a diastereoselective Petasis borono–Mannich reaction.

Glyoxylic acid-derived iminolactone **30** has also been used in a diastereoselective addition reaction to form **31** (Equation 3) [47]. Fukuyama attributed the selectivity of this reaction to attack of the nucleophile from the less hindered face of the iminium ion derived from **30**.

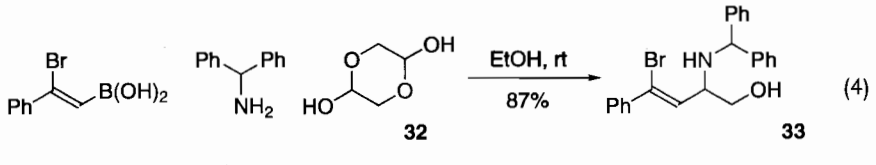


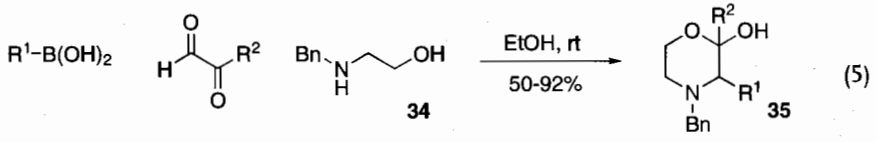
7.4.1.2 Enantioselective Addition Reactions to Glyoxylic Acid-derived Iminium Ions using Chiral Boronic Esters

The use of chiral boronic esters in the Petasis borono-Mannich reaction has been reported to result in low levels of enantioselectivity of the adducts at room temperature (6–15% ee) [48]. Auxiliaries used in this study by Scobie and co-workers included pinanediol and tartaric acid derived alkenylboronates. Morpholine was the only secondary amine used, with the primary amine ethyl glycinate failing to react.

7.4.2
Reactions of Iminium Ions Bearing α-Heteroatom Substituents

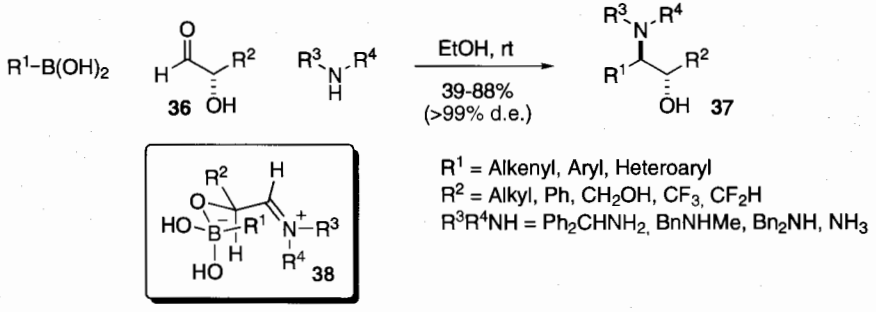
α-Hydroxy aldehydes have been successfully applied in the Petasis borono-Mannich reaction. In the simplest case, glycolaldehyde dimer **32** was used with alkenylboronic acids and primary (i.e., Ph_2CHNH_2) or secondary amines (i.e., BnNHMe) to give adducts such as **33** (Equation 4) [49]. Carboni and co-workers have shown that boronic acids react with 1,2-amino alcohols **34** and glyoxal derivatives to give 2-hydroxymorpholines **35** (Equation 5) [32]. The products were obtained in good yields as diastereomeric mixtures. The addition reactions proceed via addition to cyclic iminium ions.





7.4.2.1 Diastereoselective Addition Reactions

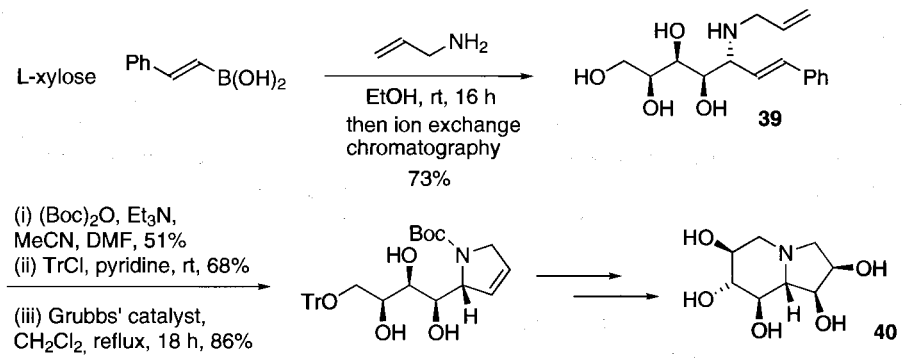
α-Hydroxy aldehydes **36** are excellent substrates for the Petasis borono-Mannich reaction [49], with reactions yielding *anti*-1,2-amino alcohols **37** with excellent levels of diastereocontrol (>99% de) (Scheme 7.9). The reaction works well with simple primary and secondary amines, and even takes place with ammonia. For adducts **37** ($R^2 = CH_2OH$) derived from glyceraldehyde, the 1,2-diol functionality can be oxidatively cleaved, as exemplified by a synthesis of (*S*)-homophenylalanine (>99% ee). Although there has been little discussion of the stereoselectivity of this reaction, a reasonable transition state model **38**, which rationalizes the formation of *anti*-1,2-amino alcohols **37**, has the iminium ion and boronate tethered in a pseudo-chair arrangement with the R^2 group adopting a pseudo-equatorial position.



Scheme 7.9 Synthesis of *anti*-1,2-amino alcohols using a diastereoselective Petasis borono–Mannich reaction.

Prakash, Petasis and Olah used this approach to synthesize *anti*-α-(trifluoromethyl)-β-amino alcohols ($R^2 = CF_3$) [50], and *anti*-α-(difluoromethyl)-β-amino alcohols ($R^2 = CF_2H$) (Scheme 7.9) [51, 52]. An example application is the single enantiomer synthesis of *anti*-difluorothreonine, which was readily obtained following *N*-deallylation and ozonolytic cleavage of the furan ring in the adduct **37** (R^1 = 2-furyl, $R^2 = CF_2H$, R^3,R^4 = allyl). Overall yields of adducts were reported to be improved by the use of recrystallized boronic acids when using commercially available samples [52].

The groups of both Petasis and Pyne have shown that the aldehyde functionality of sugars can be used in Petasis borono-Mannich reactions (Scheme 7.10) [53, 54]. Pyne and co-workers used xylose as the aldehyde coupling partner, in a reaction with allylamine and (*E*)-styrylboronic acid [54]. The conditions used for the coupling are very mild, and the hydroxyl functionalities of the xylose did not have to be protected. Product **39** was obtained in 73% yield as a single diastereomer following ion-exchange purification. The *anti*-1,2-amino alcohol stereochemical relationship of **39** is consistent with that seen in Petasis borono-Mannich reactions of other α-hydroxy aldehydes, occurring via transition state **38**. Product **39** was then elaborated to the polyhydroxylated indolizidine **40** using an olefin metathesis strategy.

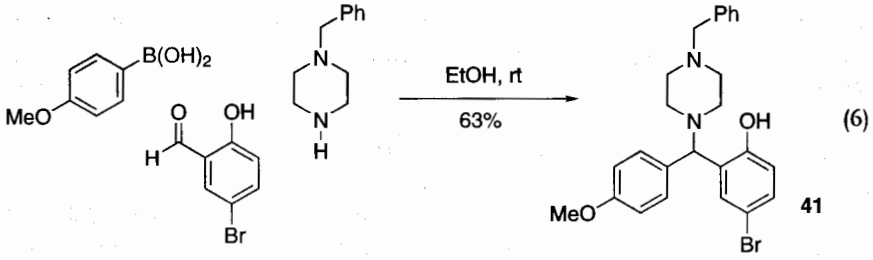


Scheme 7.10 Application of carbohydrates as the aldehyde component in the Petasis borono–Mannich reaction.

7.4.3
Reactions of Iminium Ions Bearing β-Heteroatom Substituents

Finn and Petasis have independently shown that salicylaldehyde is a suitable aldehyde for the Petasis borono-Mannich reaction, with alkenyl, aryl and heteroarylboronic acids (Equation 6) [30, 31]. The reaction works best for aliphatic secondary amines, as in the formation of **41**; primary amines give modest yields of adducts **41**. Benzaldehydes lacking ortho hydroxyl functionality do not react, with even ortho methoxy functionality being unsuitable, which is consistent with a tethering mechanism via putative intermediate **9** (Figure 7.3). Petasis and Boral reported that reactions occurred at room temperature over 24–36 h, using EtOH, MeOH or acetonitrile,

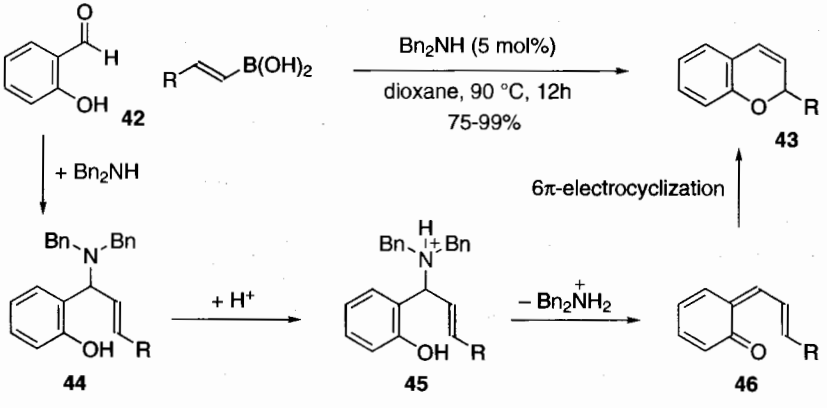
while solvents such as toluene and dichloromethane resulted in slower reactions. Wang and Finn employed dioxane as solvent at 90 °C when using morpholine as the secondary amine component.



(6)

Microwave-assisted Petasis borono-Mannich reactions of arylboronic acids, secondary amines and salicylaldehyde have been carried out in CH_2Cl_2 at 120 °C for 10 min [40]. The main problem encountered here was incomplete conversions, resulting in modest adduct yields (23–76%). The reaction of a primary amine (*p*-anisidine) under the same conditions failed to produce the desired adducts, giving instead only the imines (cf. reactions with glyoxylic acid).

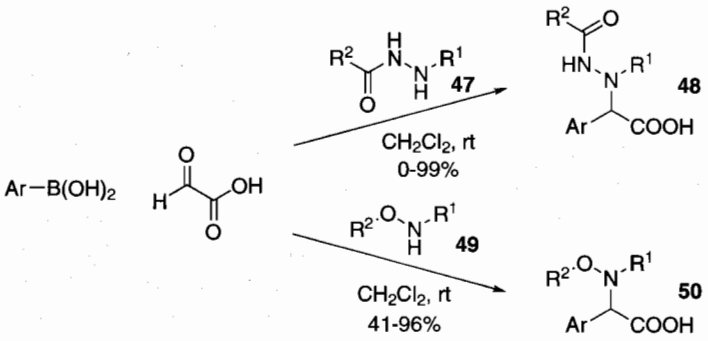
Finn also showed the formation of 2*H*-chromenes under the same reaction conditions, using alkenylboronic acids and morpholine in dioxane at 90 °C. A more convenient route to the 2*H*-chromenes was then developed using a catalytic amount of dibenzylamine in the presence of alkenylboronic acids and salicylaldehyde (**42**, Scheme 7.11) [30]. Chromenes **43** were reported to arise from the initial Petasis borono-Mannich adducts **44** via an acid promoted intramolecular S_N2' attack of the ortho-hydroxyl group onto the protonated allylic amine of intermediate **45**. A more likely mechanism involves elimination from **45** to intermediate **46**, followed by 6π-electrocyclization to the product. The reaction is tolerant of various functional groups and substitution patterns on the salicylaldehyde, and could also be promoted using a polymer-supported base, such as Merrifield resin-supported dibenzylamine (40–50 mol%) [30].



Scheme 7.11 Synthesis of 2*H*-chromenes using a Petasis borono–Mannich reaction.

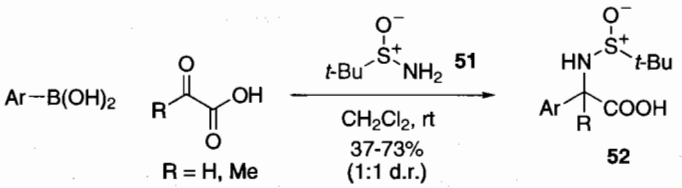
7.4.4
Addition Reactions using Iminium Ions Derived from Hydrazines, Hydroxylamines and Sulfinamides

Portlock and co-workers demonstrated that Boc and Cbz protected hydrazines **47** undergo regioselective addition with glyoxylic acid and aryl or heteroarylboronic acids at room temperature (Scheme 7.12) [55]. Three-component coupling only occurred when the hydrazide nitrogen atom undergoing condensation with the glyoxylic acid was N-substituted (R = alkyl, Bn, CH_2COOR, aryl) to give adducts **48**. Unsubstituted hydrazides **47** (R^1 = H) could, however, be reacted by pre-forming the hydrazones (e.g. BocNHN=CHCOOH), and then reacting with arylboronic acids. The resultant unsubstituted adducts **48** (R^1 = H) were of interest as combinatorial library precursors, and could also be formed by catalytic hydrogenation of the benzyl adducts (R^1 = Bn). Naskar et al. have reported the similar use of arylboronic acids, alkyl hydroxylamines **49** (R^1 = H, Me; R^2 = Me, Bn, *t*-Bu) and glyoxylic acid in Petasis borono-Mannich reactions to give **50** (Scheme 7.12) [56].



Scheme 7.12 Application of hydrazides and alkyl hydroxylamines in the Petasis borono–Mannich reaction.

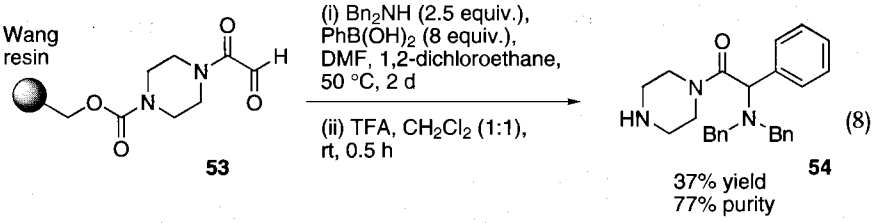
Naskar et al. have also reported the use of sulfinamides **51** in Petasis borono-Mannich reactions (Equation 7) [56]. Products **52** were obtained in good yields, but as 1:1 mixtures of diastereomers. The reaction was also accomplished using pyruvic acid, representing an unusual example of an enolizable ketone in a Petasis borono-Mannich reaction.



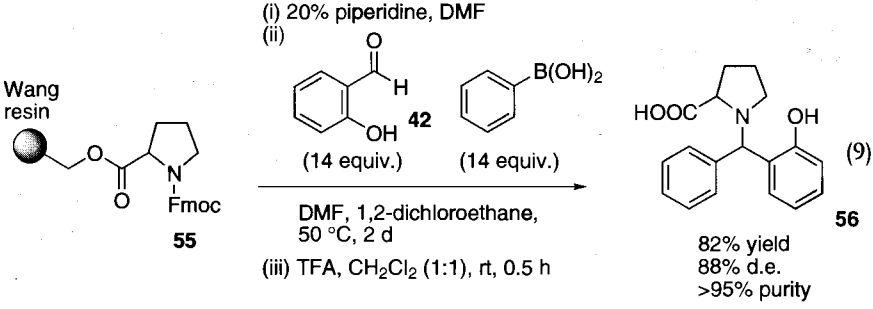
(7)

7.5
Polymer-supported Petasis Borono-Mannich Reactions

Several groups have reported the use of solid-phase (polymer-supported) variants of the Petasis borono-Mannich reaction, and examples are known in which each of the three components are polymer-supported. An advantage of the use of supported reagents is the ability to drive reactions to completion by the use of excess solution-phase reagents. Hansen and co-workers have demonstrated a series of examples in which each of the three components were attached to a polymer support [33]. Reaction of a Wang resin-supported glyoxylic acid **53** (attached to the resin via an amide or ester linkage) with secondary amines and arylboronic acids gave moderate yields of products **54** (Equation 8).

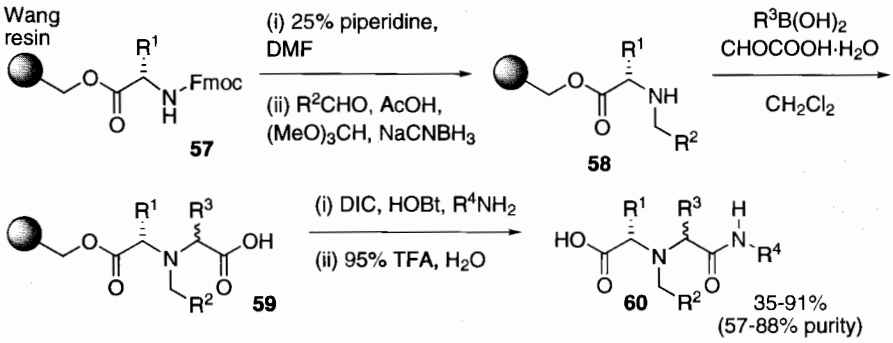


Several groups have reported the use of polymer-supported amines in the Petasis borono-Mannich reaction. Hansen also used Wang resin supported piperazine or proline in coupling reactions with arylboronic acids and glyoxylic acid or salicylaldehyde [33]. Reactions with Wang supported piperazine (attached via a carbamate linkage) gave products in good yields and purities following cleavage. Reactions with Wang supported Fmoc-proline **55** (attached via an ester linkage) gave products **56** in good yields and purities following cleavage, but with varying degrees of diastereoselectivities (8–95%) (Equation 9).



Klopfenstein and co-workers outlined a solid-phase route to the synthesis of peptide mimetics using the Petasis borono-Mannich reaction [57]. In this study, a Wang resin supported Fmoc-protected amino acid **57** (attached via an ester linkage) was first reductively aminated to give a secondary amine **58**, which was then reacted with

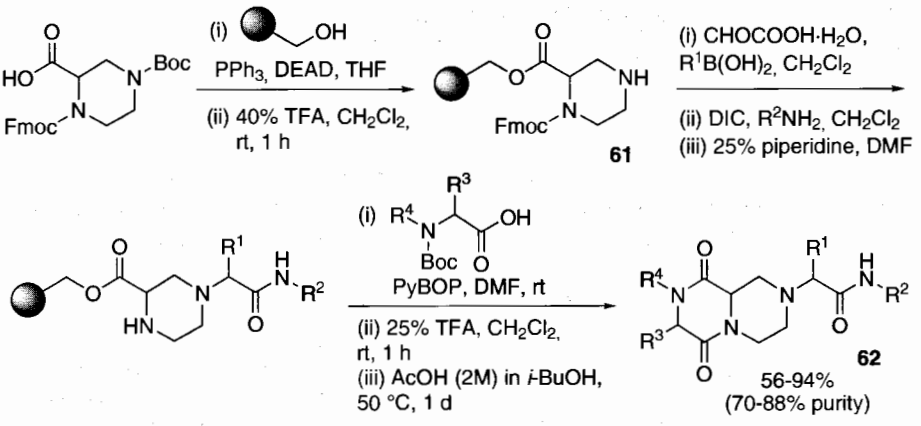
arylboronic acids and glyoxylic acid to give **59** (Scheme 7.13). Dichloromethane was the solvent of choice due to its excellent resin-swelling capability. Carboxylic acid products **59** were then coupled with primary amines using standard amide-bond forming conditions (DIC/HOBt), and the products cleaved from the resin using TFA. The poor de of each final product **60** presumably reflects a non-stereoselective Petasis borono-Mannich step. Although few examples were given, the authors allude to the utility of the process in a high-throughput fashion, using 96-well reaction blocks, for the creation of peptide mimetics.



Scheme 7.13 Application of polymer-supported amines in the Petasis borono–Mannich reaction.

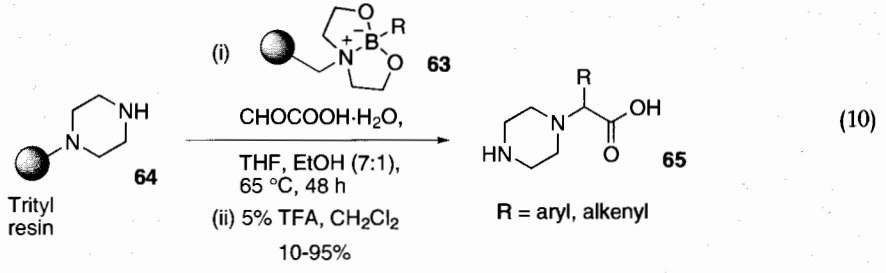
Golebiowski and co-workers have developed a synthesis of peptide β-turn mimetics using a strategy involving sequential Petasis borono-Mannich and diketopiperazine formation (Scheme 7.14) [58]. In this approach, the supported piperazine **61** (attached via an ester linkage to hydroxymethylpolystyrene resin) underwent Petasis borono-Mannich reaction with glyoxylic acid monohydrate. This was followed by DIC coupling with an amine, Fmoc deprotection and coupling with Boc-protected amino acids. Rather unsurprisingly, poor diastereoselectivities were obtained for the Petasis borono-Mannich reactions. The ester linkage with the resin is robust but, following acidic deprotection of the newly installed Boc protected amine functionality, cyclization onto the ester linkage releases the diketopiperazine products **62** from the resin. Again, although few examples were reported, the authors state that the approach is amenable to high-throughput synthesis, with products obtained in good yields and purities (70–88%).

Thompson and Hall have shown that polymer-supported secondary amines will participate in the Petasis borono-Mannich reaction [59, 60]. This approach uses an example of "resin-to-resin" transfer, in which the boronic acid component **63** is initially attached via an ester linkage with polystyrene-supported diethanolamine. Transesterification of **63** by ethanol releases the corresponding diethylboronate, which then reacts in situ with polymer-supported tritylpiperazine **64** and glyoxylic acid (Equation 10). Cleavage from the resin occurred under mild conditions to give products **65**, which were obtained in good yields and purities when using electron-rich aryl-

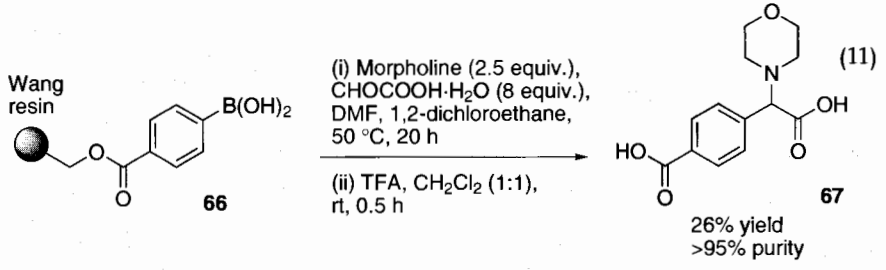


Scheme 7.14 Application of polymer-supported piperazines in the Petasis borono–Mannich reaction.

boronates and alkenylboronates. The process was also suitable for use with other secondary amines.



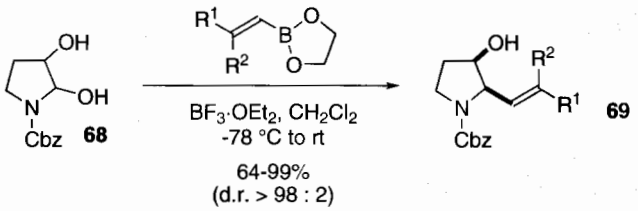
The boronic acid component can also be attached directly to the resin, as shown by Hansen and co-workers [33]. A Wang-resin supported arylboronic acid (**66**) was coupled with either glyoxylic acid or salicylaldehyde and secondary amines (Equation 11). Products were obtained in high purities but low yields (as for **67**), a factor that may be due in part to the electron-deficient nature of the supported arylboronic acid.



7.6
Other Types of Addition Reactions

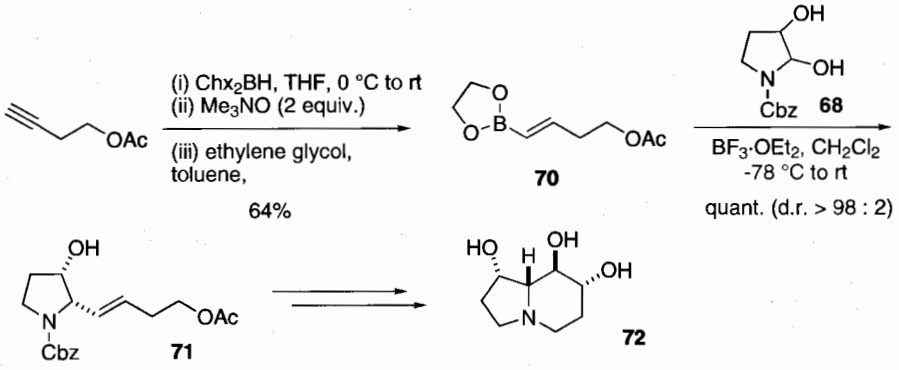
7.6.1
Lewis Acid Promoted Additions: Addition Reactions to N-Acyliminium Ions

Batey and co-workers have reported the addition of alkenyl and arylboronic acids to N-acyliminium ion precursors in the presence of Lewis acids (Equation 12) [61]. Specifically, substrates able to generate an endocyclic iminium ion, in which the nitrogen atom has an exocyclic carbamate substituent, were suitable precursors. Various boronic esters as well as boronic acids undergo addition in the presence of $BF_3 \cdot OEt_2$. The requirement for a Lewis acid strongly implies the intermediacy of an N-acyliminium ion. Most studies were undertaken with the diol **68**, leading to the substituted products **69** in high yield and excellent *cis*-diastereoselectivity. This is one of the only studies in which both the (*E*)- and (*Z*)-alkenylboron compounds were confirmed to add in a stereospecific manner (i.e. with retention of the alkene geometry). Replacement of the 3-hydroxy substituent of **68** by a methoxy or fluorine substituent was well tolerated, but replacement by a hydrogen substituent (i.e. for the 3-unsubstituted precursor) resulted in a lower product yield (25%), perhaps because of competing proton loss from the N-acyliminium ion. The reaction also occurs with piperidine- and tetrahydroquinoline-based systems.



(12)

This method has been applied to the synthesis of polyhydroxylated indolizidines [62]. For example, alkenylboronate ester **70**, prepared by hydroboration of 1-acetoxybut-3-yne, underwent highly diastereoselective addition to the diol **68** in the presence of $BF_3 \cdot OEt_2$ (Scheme 7.15). Elaboration of the alkene functionality of **71** by dihydroxylation, followed by a cyclization approach using reductive amination led to the target molecule 6-deoxycastanospermine (**72**).



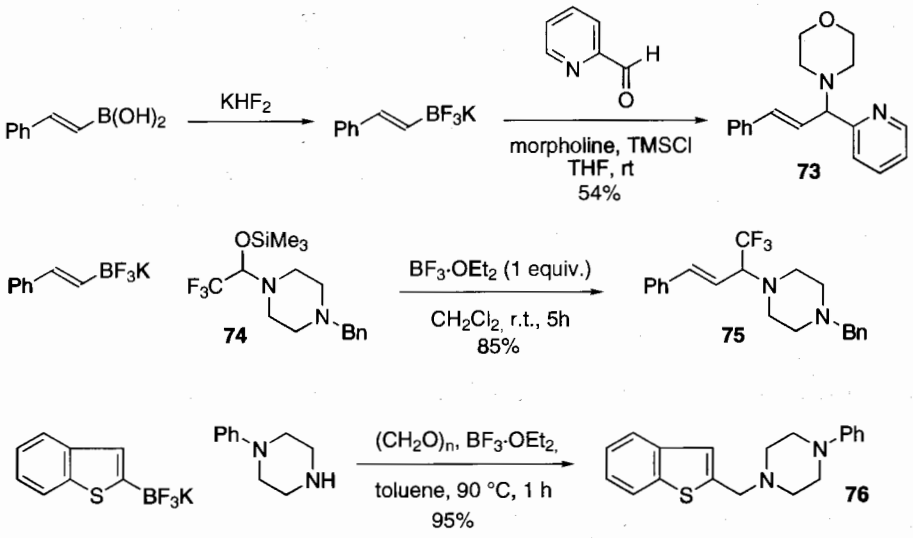
Scheme 7.15 Total synthesis of 6-deoxycastanospermine using the N-acyl iminium ion variant of the Petasis borono–Mannich reaction.

7.6.2
Lewis Acid Promoted Additions of Organotrifluoroborate Salts

Three groups have reported the use of alkenyl or aryltrifluoroborate salts [63] in Petasis borono-Mannich reactions. Bryce and Hansen demonstrated the reaction of potassium styryltrifluoroborate, morpholine and pyridine-2-carboxaldehydes to give **73** (Scheme 7.16) [64]. The styryltrifluoroborate anion is probably not the nucleophile, since TMSCl was used as an additive, which had previously been shown, by Vedejs, to generate organodifluoroboranes [65]. Billard and Langlois have used silylated fluorinated hemiaminal derivatives **74** and potassium styryltrifluoroborate in the presence of stoichiometric $BF_3 \cdot Et_2O$ to generate **75** (Scheme 7.16) [66]. The groups of Kaufmann and Batey had previously applied $BF_3 \cdot Et_2O$ as a Lewis acid with organotrifluoroborate salts [67–69]. Raeppel and co-workers have also demonstrated the use of $BF_3 \cdot Et_2O$ (25 mol%) to promote the additions of aryl, alkenyl and allyltrifluoroborate salts with secondary amines and various aldehydes, as in the synthesis of **76** (Scheme 7.16) [19]. A range of other Lewis acids were also shown to promote addition, including Zn(II), Cu(II), Sn(II), Ln(III) and Sc(III) triflate, $MgBr_2 \cdot OEt_2$ and TiF_4. Addition of acetic acid led to an improvement in the yields of adducts derived from electron-poor aryltrifluoroborates.

For Petasis borono-Mannich reactions of formaldehyde, methylation of the amine reportedly occurs as a side-reaction, presumably by iminium ion reduction [19]. The hydride source under these conditions may be formic acid, as in the Eschweiler–Clarke methylation reaction. This problem was overcome by the use of potassium trifluoroborate salts and Lewis acids in toluene at 90 °C (the reaction in highly polar solvents such as acetonitrile, DMF and DMSO gives the reduction product).

Kabalka and co-workers have shown that alkynyltrifluoroborate salts undergo coupling with secondary amines and salicylaldehydes (or formaldehyde) in an ionic liquid solvent at 80 °C [70]. The ionic liquid undoubtedly helps solubilize the trifluo-

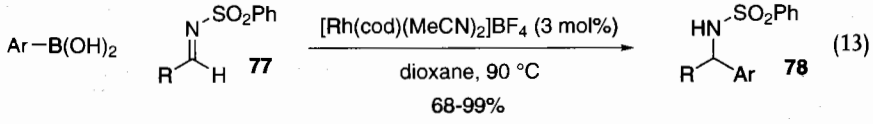


Scheme 7.16 Application of trifluoroborate salts in the Petasis borono–Mannich reaction.

roborate salt, and may help facilitate ligand exchange and nucleophilic activation of the alkynyltrifluoroborate anion by the ortho-hydroxyl group of the salicylaldehydes.

7.6.3
Rhodium-catalyzed Additions of Boronic Acids to N-Sulfonylimines

Rhodium catalysts have been widely used for C–C bond formation processes [71]. Particularly noteworthy are the Rh(I)-catalyzed additions of boronic acids and their derivatives to α,β-unsaturated carbonyl compounds [72–78] and aldehydes [75, 79] (Chapter 4). The groups of Miyaura and Hayashi have shown that Rh(I) catalyzes the addition of sodium tetraphenylborate and arylstannanes to N-sulfonylimines [80–82]. Miyaura and co-workers have also reported the first example of a Rh(I)-catalyzed addition of an arylboronic acid to an N-sulfonylimine (**77**), to give sulfonamide **78** (Equation 13) [83]. Reactions proceeded with 2 equivalents of arylboronic acids using either a cationic Rh(I) catalyst alone, or in combination with appropriate phosphine ligands such as bis(diphenylphosphino)propane or P(*i*-Pr)$_3$. Boronic esters will also react, particularly in the presence of triethylamine. The reaction does not proceed with simple aldimines, such as PhCH=NPh.



(13)

The mechanism for the reaction may involve a process analogous to that proposed in additions to aldehydes and enones (Figure 7.4). The arylboronic acid undergoes transmetallation with the catalyst to produce an aryl–Rh(I) species **79**. Insertion of the sulfonylimine **77** to give **80**, followed by hydrolysis would then lead to the product **78** and regenerate the active Rh(I)–OH species **81** used in the transmetallation. Since water is not used as an additive, this mechanism assumes the presence of adventitious water. An alternative mechanism, which does not include water, could involve direct transmetallation of the boronic acid by Rh(I)–N species **80**.

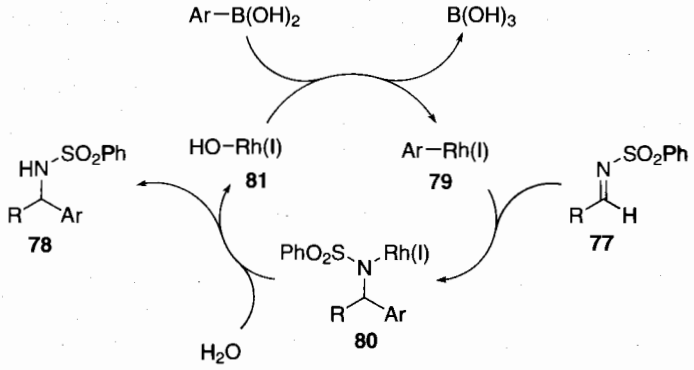
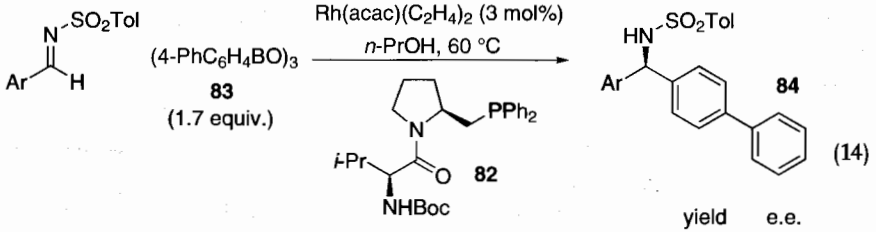


Figure 7.4 Plausible mechanism for the Rh(I) catalyzed addition of arylboronic acids to N-sulfonylimines.

A catalytic enantioselective variant of the reaction has been described recently by Tomioka and co-workers [84]. Chiral amidophosphanes such as **82** were employed in the presence of Rh(I) for the addition of arylboroxines **83** (Equation **14**). Arylboronic esters gave diminished yields. Ortho substituents on the N-tosylarylimine are important for achieving useful levels of enantioselectivity in the products **84**. An ortho trimethylsilyl substituent was particularly effective for achieving high levels of enantioselectivity. The ortho-TMS functional group was further manipulated through protodesilylation (using CsF, aqueous DMF) or iododesilylation (using ICl).



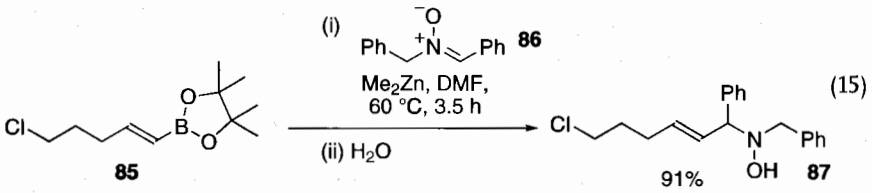
(14)

	yield	e.e.
Ar = 4-MeC_6H_4	86%	72%
Ar = 3-MeC_6H_4	90%	76%
Ar = 2-MeC_6H_4	97%	86%
Ar = 2-$Me_3SiC_6H_4$	98%	92%

7.6.4

Dialkylzinc-promoted Additions of Alkenylboronic Esters to Nitrones

Chavant and Vallée have demonstrated dialkylzinc-promoted addition of pinacolyl alkenylboronates to nitrones (Equation 15) [85]. The reaction is tolerant of chloro and pivalate ester functionality on the alkenylboronate **85**. Nitrones **86** derived from aromatic aldehydes with either N-benzyl or N-alkyl functionality were mainly used, although two examples employing nitrones derived from enolizable aliphatic aldehydes were also reported. The addition protocol is thought to rely on a transmetallation of the pinacolyl alkenylboronates with dimethylzinc to give alkenylzinc species, which then undergo addition to give products such as **87**. The use of diethylzinc resulted in some competitive direct ethylation of the nitrones. ^{1}H and ^{11}B NMR studies indicate that transmetallation is the rate-determining step, with the disappearance of the dimethylzinc, alkenylboronate and nitrone signals occurring simultaneously with the formation of pinacolyl methylboronate. The intermediacy of either pinacolyl alkenylmethylborate complexes or free-radicals is also possible. The same conditions were reported to be inapplicable to additions to simple imines.

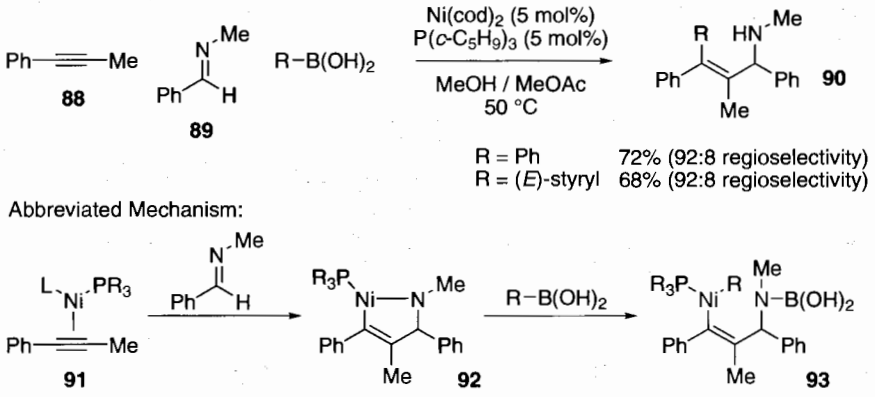


(15)

7.6.5

Nickel-catalyzed Couplings of Boronic Acids with Alkynes and Imines

Patel and Jamison have shown that phenyl and (*E*)-styrylboronic acid undergo a novel three-component coupling reaction with internal alkynes **88** and imines **89** in the presence of Ni(0) catalysts to give adducts **90** (Scheme 7.17) [86]. The reaction was reported to be more efficient than the corresponding addition of triethylborane, and does not occur with more reactive imines, such as sulfonylimines. Addition across the alkyne occurs in an exclusively *syn*-stereoselective manner, and with good levels of regiocontrol. Direct adducts of the imine and boronic acid were not formed under the reaction conditions. Based upon the mechanism for the similar addition of triethylborane suggested by Jamison, a likely mechanism involves imine insertion into an η^2-Ni(0) alkyne complex (**91**) to give an azametallocyclopentene (**92**). Transmetallation of **92** by the boronic acid would then give the Ni(II) species **93**, which on reductive elimination and protonation would lead to adduct **90**. Methanol as co-solvent may serve to facilitate either transmetallation or the subsequent reductive elimination–protonation steps.



Scheme 7.17 Ni-catalyzed coupling of boronic acids, imines and alkynes.

7.7 Concluding Remarks

The addition of organoboronic acids and their derivatives to imines and iminium ions has emerged as an important new approach toward the synthesis of amines. Seminal observations by Petasis on the boronic acid variant of the Mannich reaction provided the early impetus for this field. The reactions occur under mild conditions, are unaffected by the presence of water, and tolerate a wide range of functional groups. The approach is particularly valuable for small molecule library synthesis, given the three-component nature of the reaction and the commercial availability of many boronic acids. Alkenyl, aryl and heteroarylboronates all undergo reaction, with most examples using paraformaldehyde, glyoxylic acid, α-hydroxy aldehydes or salicylaldehydes. The development of Lewis acid, rhodium, nickel and zinc based reactions has allowed an even greater range of substrate classes to be utilized. Complex heterocycles, natural products and other targets have also been synthesized using this strategy. This growing field will undoubtedly develop further, and it seems clear that this will remain an important use for boronic acids.

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8
(α-Haloalkyl)boronic Esters in Asymmetric Synthesis

Donald S. Matteson

8.1
Introduction

The utility of (α-haloalkyl)boronic esters in asymmetric synthesis results from a unique combination of several features of their chemistry. A wide variety of products can be obtained in very high stereopurity, and the reactions are compatible with a considerable variety of functional substituents, provided that OH and NH groups are masked. Stereospecific displacement of halide from an (α-haloalkyl)boronic ester with a nucleophile yields an asymmetric boronic ester, which can either be converted stereospecifically into another product such as an alcohol or put into another cycle of reaction with (dihalomethyl)lithium to install additional stereocenters. The general synthetic utility of these boronic esters can best be understood from a detailed outline of the general processes involved.

The most useful biological applications of these compounds have included the synthesis of some asymmetric insect pheromones in very high stereopurity, described in Sections 8.3.1 and 8.3.3, and the proteasome inhibitor "Velcade™" (bortezomib) developed by Millennium Pharmaceuticals and recently approved by the United States FDA as well as the European Union for treatment of relapsed and refractory multiple myeloma, Section 8.3.6.

8.2
General Description of (α-Haloalkyl)boronic Ester Chemistry

8.2.1
A Brief History of Boronic Ester Chemistry

First, simple achiral boronic acids and esters are readily available from various sources (Chapter 1). The first synthesis from an organozinc reagent preceded general acceptance of Avogadro's hypothesis [1], and was superseded nearly a century ago by the now standard preparation from Grignard reagents [2, 3]. Hydroboration has

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been known for half a century [4], and several variants are particularly useful for boronic ester synthesis [5, 6], including several asymmetric examples [7].

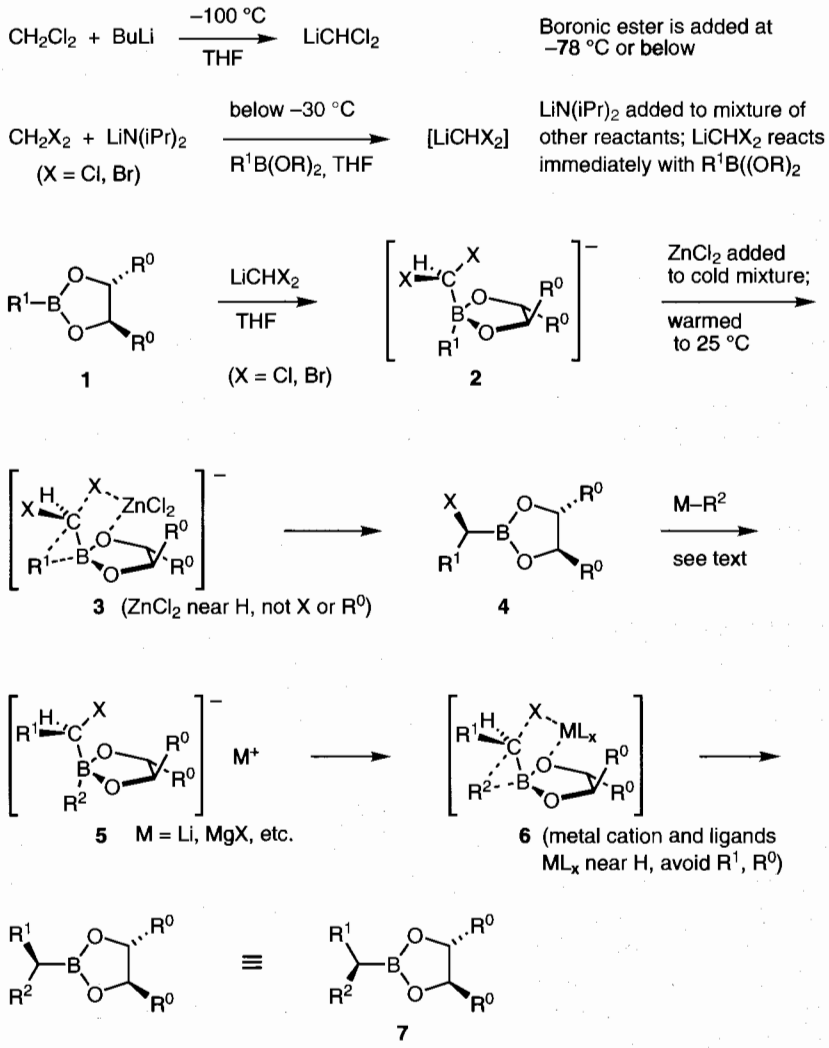
The first synthesis of an (α-haloalkyl)boronic ester [8], a free radical addition of a tetrahalomethane, was followed by mechanistic studies that indicated the potential for stereospecific alkylation with Grignard reagents via borate intermediates [9], if only there had been a way to obtain asymmetric examples. The discovery of the efficient reaction of (dichloromethyl)lithium with boronic esters to form (α-chloroalkyl)boronic esters by insertion of a CHCl group into the B–C bond opened a new opportunity [10]. Boronic esters of pinanediol, prepared from (+)-α-pinene by osmium tetroxide catalyzed oxidation, were soon found to undergo the insertion reaction with a strong asymmetric bias, with diastereomeric selectivities frequently in the 90–95% range [11]. It was subsequently found that anhydrous zinc chloride promotes the reaction and increases diastereoselectivity to as high as 99.5% in some cases [12].

The (dichloromethyl)lithium insertion reaction or its bromo analog provides most of the (α-haloalkyl)boronic esters of interest in this chapter, and is described in detail in the next section. (Halomethyl)boronic and (2-bromo-2-propyl)boronic esters require different approaches and are described under Section 8.3.2.

8.2.2
C_2-symmetrical Boronic Esters

Although pinanediol boronates were discovered first, chiral directors having C_2 symmetry can provide better stereocontrol. They are also simpler to interpret because both faces of the trigonal boron atom are identical. The reaction of a boronic ester of an enantiopure 1,2-diol (**1**) and a (dihalomethyl)lithium forms a borate complex (**2**) that is stable at low temperatures (Scheme 8.1). A Lewis acid, preferably zinc chloride, participates in the postulated transition state (**3**) and leads to formation of the (α-haloalkyl)boronic ester (**4**) in high stereopurity (often ~99% a single isomer). Transition state **3** is favored over alternatives because, apparently, of steric repulsion between the ligands on the zinc atom and both the bulky R^0 group and the nearest atom on the $CHCl_2$ group, which disfavors a parallel chlorine atom.

Reaction of **4** with a nucleophilic reagent, designated here as M–R^2, where M is a metallic cation and R^2 is a nucleophile, leads to borate complex **5**. Variants of M–R^2 include organolithium and Grignard reagents, alkali metal alkoxides, lithium disilylamides, and several others. In transition state **6**, R^1 avoids proximity to the ligands on the metal cation. The similarity of transition state **6** to transition state **3** is significant because it can result in a second diastereoselection and a stereopurity of >99.8% in some cases [13]. The final product is the boronic ester 7, which is a special case of boronic ester **1** and can be put back through a similar sequence to form another stereocenter. In principle, there is no limit to the number of adjacent stereocenters that can be installed in this manner, though it is not generally practical to go beyond three or four.



Scheme 8.1 General assembly of asymmetric carbon chains from boronic esters of C_2-symmetrical diols.

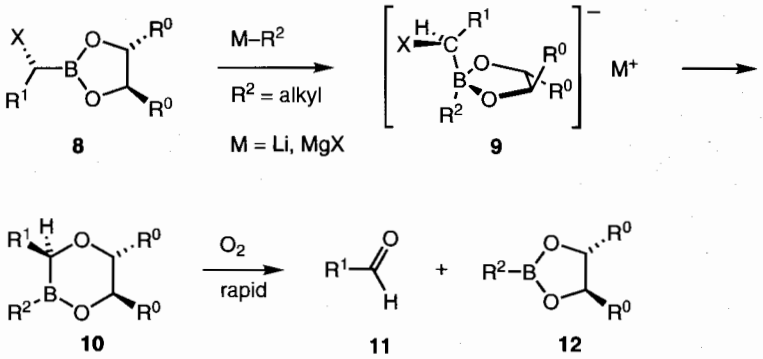
Several other features of the chemistry outlined in Scheme 8.1 are worthy of further comment:

1. Borate complex **2** does not rearrange under the conditions of its formation, generally below –20 °C. This prevents multiple insertions of $LiCHX_2$ with consequent formation of mixtures or polymers.
2. Reaction of a C_2-symmetrical diol ester of a (dihalomethyl)boronic acid with an alkyllithium or Grignard reagent will yield the same borate anion **2** as that from the corresponding alkylboronic ester **1** with a (dihalomethyl)lithium.

3. Zinc chloride is the usual Lewis acid promoter of the rearrangement of borate **2** into (α-haloalkyl)boronic ester **4**. However, lithium cation functions in the same capacity if zinc chloride is not added, but usually does not provide optimum stereoselection. One factor in favor of the zinc chloride is that it sequesters chloride as $ZnCl_3^-$ or $ZnCl_4^{2-}$, thus slowing epimerization of the product **4** by free chloride ion [14].
4. The binding of the nucleophile R^2 to the boron atom in structure **5** facilitates the internal migration and nucleophilic displacement with inversion to the point that side reactions such as β-elimination are not observed. Strongly basic nucleophiles work best in the conversion of **4** into **7**, but the displacement process is assisted by the boron atom even if a fully covalent bond to boron is probably not involved [9].
5. Any second significant diastereoselection in the conversion of **4** into **7** requires a strongly basic nucleophile that binds irreversibly to boron and a chiral directing group that has C_2 symmetry [13]. Pinanediol, the most inexpensive known useful chiral director, lacks C_2 symmetry and is described separately.
6. Weakly basic atoms, especially halides, cannot be present in the β-position of **1** or **4**, because elimination of such species together with the boronic ester function is rapid in the presence of any reagent as basic as water [15].
7. Transition state structures **3** and **6** accord with quantum mechanical calculations [16]. The stereodirection is also in accord with that observed in reactions bearing some analogy [17].
8. In structure **7** the most recently introduced substituent R^2 is written as pointing toward the viewer and downward, and the downward R^0 group of the chiral director also points toward the viewer. This feature serves as a convenient mnemonic for the favored isomer. If the molecule is rotated 180° around the horizontal axis, R^2 will point upward and, like the upward pointing R^0, away from the viewer.
9. R^0 groups should be saturated hydrocarbon units such as isopropyl or cyclohexyl [18, 19]. If R^0 = phenyl or 1-methoxy-1-methylethyl, stereoselectivities are poor [19, 20]. Marginally satisfactory stereodirection has been achieved with $R^0 = CH_3$ [21], and similar levels have been seen with dicyclohexylidenemannitol [22].
10. Reactions of boronic esters (**1**) with (dihalomethyl)lithium have been optimized for R^1 = alkyl, but not for R^1 = aryl or alkenyl, which migrate much faster. A few examples of the latter are described in Section 8.3.

Direct evidence for the second diastereoselection was obtained when an α-chloroboronic ester **8** diastereomeric to **4** was prepared and treated with a Grignard reagent. The first product isolated was the boronic ester **12** (Scheme 8.2) [13]. The initial product was then shown to be a borinic ester (**10**), which undergoes air oxidation extremely readily and forms aldehyde **11** as well as boronic ester **12**. These products usually differ grossly in molecular weight from the major product **7** derived from **4** and are easily separated, leaving **7** in extreme diastereopurity. Evidently, the unexpected behavior of intermediate borate **9** results because the halide X is sterically inaccessible to displacement by the alkyl group R^2. Rotation of the R^1CHX group to al-

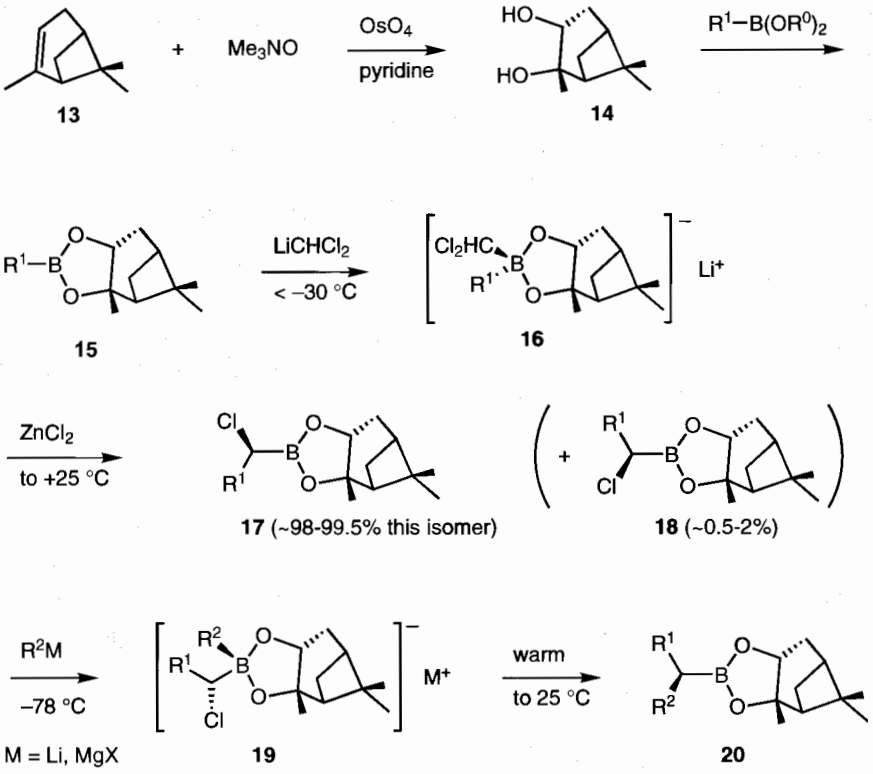
low displacement of X by R^2 would force an assisting metal cation into proximity to either R^1 or R^0. As a result of these steric repulsions, the oxygen atom migrates preferentially in spite of the general thermodynamic preference for migration of carbon rather than oxygen, which was recognized long ago [9]. This difference in behavior between **4** and **8** was also shown to result in kinetic resolution [13].



Scheme 8.2 General reaction of minor isomer of C_2-symmetrical (α-haloalkyl)boronic esters with nucleophiles.

Pinanediol is the least expensive of the useful chiral directors. α-Pinene (**13**) reacts with trimethylamine *N*-oxide and osmium tetroxide catalyst in the presence of pyridine and water to produce pinanediol (**14**) (Scheme 8.3) [23, 24]. A kinetic study has shown that the reaction is first-order in trimethylamine *N*-oxide, first-order in osmium tetroxide, and zero-order in α-pinene [25]. Trimethylamine *N*-oxide produced better yields than the less expensive *N*-methylmorpholine *N*-oxide [24, 26]. Although the first reported solvent was *tert*-butyl alcohol [24], acetone can be used instead [26, 27]. The reflux temperature of *tert*-butyl alcohol is a little too high, and some over-oxidation to hydroxyketone occurs above about 75 °C. Refluxing in acetone avoids over-oxidation but is slower. Two moles of pinene with a small excess of trimethylamine *N*-oxide and 1 g of osmium tetroxide produce pinanediol in 95–96% yield in 3–4 days in *tert*-butyl alcohol, or after about a week in acetone [24, 27].

Pinanediol has several practical advantages as a chiral director. Both enantiomers of α-pinene are readily available. Although their enantiopurities from convenient natural sources are only in the 80–95% range, pinanediol can be purified by recrystallization from heptane [26]. The rigid structure of pinanediol fits the steric requirements for bonding to boron very closely, with no significant entropy cost for forming the cyclic derivative. Consequently, pinanediol boronates (**15**) are exceptionally stable boronic esters, which are easily purified by chromatography. The only problem is that they can be too stable when there is need for cleaving the pinanediol, but several ways have been found to take care of this problem (Section 8.4.1). With very small alkyl groups on boron, especially methyl, pinanediol boronic esters do not provide the best stereocontrol, but with larger groups pinanediol boronic esters may undergo the (dichloromethyl)lithium insertion reaction when other esters fail.

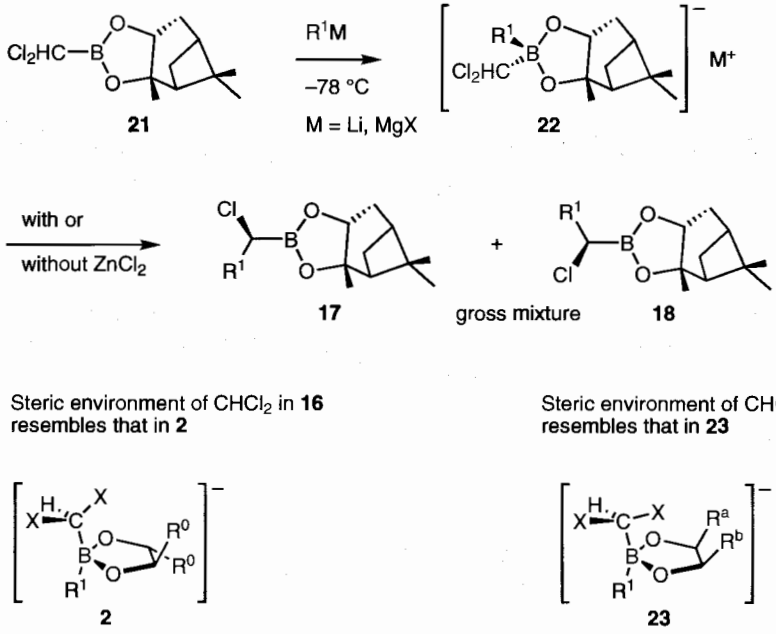


Scheme 8.3 General assembly of asymmetric carbon chains via pinanediol boronic esters. Structures **13**–**20** are drawn as slightly distorted planar projections of a three-dimensional computer model of the rigid terpenoid unit. For detailed reaction conditions, see Scheme 8.1.

A limitation of pinanediol boronic esters (**15**) results from the difference between the two diastereotopic faces of the trigonal boron atom. The sequential double diastereodifferentiation observed with chiral directors having C_2-symmetry is not possible. Borate anion **16** derived from **15** rearranges to (α-chloroalkyl)boronic esters **17** and **18** in a ratio that usually exceeds 50:1 (Scheme 8.3) [12]. Alkylmetallic reagents attack **17** from the less hindered side to form **19**, in which the chloride to be displaced is not in a comparable steric environment to that in **16** [28]. The major diastereomer **20** is produced in about the same proportion as its precursor **17** (Scheme 8.3).

Pinanediol (dichloromethyl)boronate (**21**) is not a useful asymmetric reagent in reactions with organolithium or Grignard reagents (Scheme 8.4) [28]. The ratio of diastereomers **17** and **18** varies according to the substituent R^1 and whether zinc chloride is used, but does not strongly favor either isomer. The reason appears fairly obvious, inasmuch as the $CHCl_2$ group in borate intermediate **16** (Scheme 8.3) is similar to that in **2** (Schemes 8.1 and 8.4), and provides strong diastereodifferentiation. The $CHCl_2$ group in borate **22** lies in a pseudo meso environment that is weakly stere-

odifferentiated, as illustrated by **23** (Scheme 8.4). The same effects apply to the borate intermediate **19** derived from **17** and its diastereomer derived from **18**, both of which can rearrange easily via R^2 migration.



Scheme 8.4 Lack of diastereoselectivity in reactions of pinanediol (α-chloroalkyl)boronates.

8.3
Boronic Ester Intermediates in Synthesis

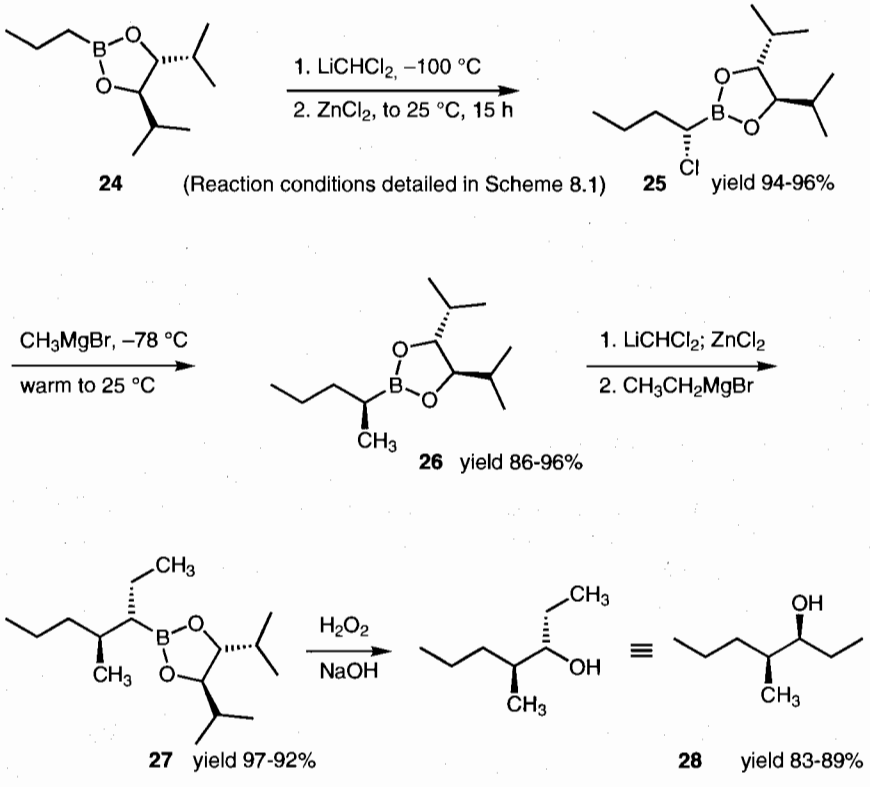
8.3.1
Boronic Ester Intermediates without Functional Substituents

The reaction of boronic esters with (dihalomethyl)lithium is particularly well suited to the building of asymmetric structures in which there are no functional substituents. At the end of the synthesis, the boronic ester group can be replaced by reaction with hydrogen peroxide to form the corresponding asymmetric secondary alcohol [11, 12, 29].

The first test of pinanediol (α-chloroalkyl)boronic ester chemistry included syntheses of (2*S*,3*S*)- and (2*R*,3*S*)-3-phenyl-2-butanol, each in 94–96% diastereopurity and, assuming independent stereoselection for installation of each of the two adjacent stereocenters, >99% enantiopurity [11]. These targets were chosen because their absolute configurations had been established by Cram's classic work [30]. Zinc chloride catalysis had not been discovered, and other features of the syntheses are also ob-

solete, and accordingly this synthesis is not reviewed in detail. The one observation that is still relevant is that the rearrangement of the borate anion from pinanediol phenylboronate and (dichloromethyl)lithium is complete within an hour at 0 °C, much faster than the usual migrations of alkyl groups, and that longer reaction times or higher temperatures appear to be deleterious to diastereoselectivity.

A more interesting installation of two adjacent stereocenters is provided by the synthesis of the four stereoisomers of 4-methyl-3-heptanol in ultrahigh stereopurity [13]. The (3*S*,4*S*)-isomer (**28**) is a component of the pheromone of the elm bark beetle *Scolytus multistriatus* and had been synthesized previously from pinanediol propylboronate [29]. Either pure enantiomer of C_2-symmetrical diol 1,2-diisopropyl-1,2-ethanediol ("DIPED") can be prepared from the corresponding tartaric acid [31]. DIPED propylboronate (**24**) provided at least 500:1 diastereoselection in the conversion into the intermediate (1-methylbutyl)boronic ester **26** via the (1-chlorobutyl)-boronic ester **25** as the result of sequential double diastereoselection (Scheme 8.5) [13]. A second insertion of (dichloromethyl)lithium, ethylation with a Grignard reagent to form boronic ester **27**, and peroxidic oxidation yielded the pheromone **28**. The diastereopurity of **28** estimated by ^{13}C NMR was 99.86%, and by gas chromatography 99.8% [31], which requires that the diastereoselectivity for formation of **26** from

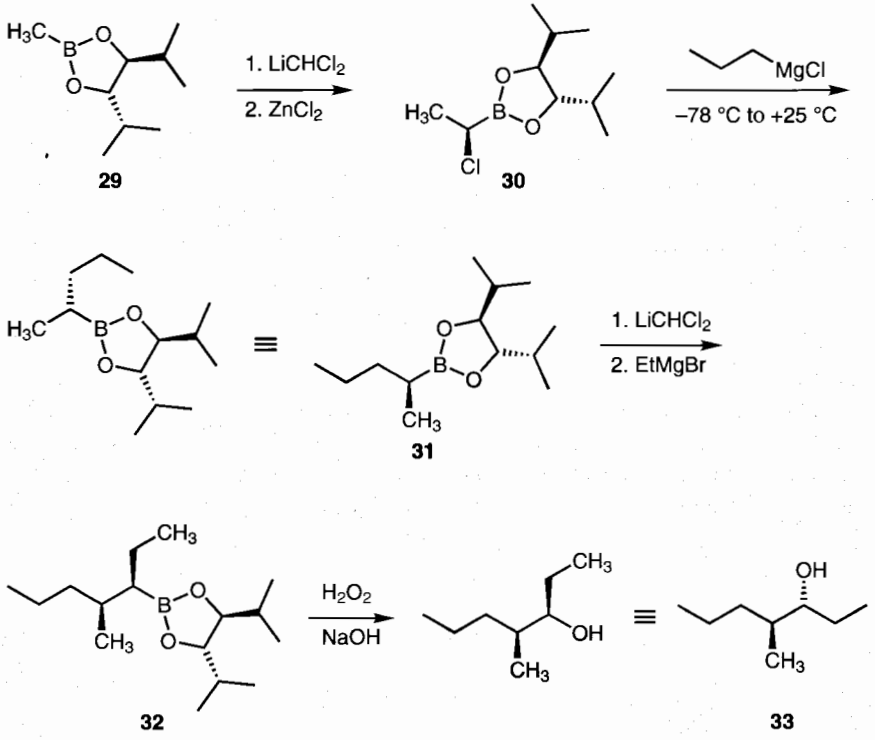


Scheme 8.5 Synthesis of (3*S*,4*S*)-4-methyl-3-heptanol in high stereopurity.

24 and **27** from **26** is at least 500:1 in both cases, and the diastereoselectivity in one or both sequences has to be at least 1000:1.

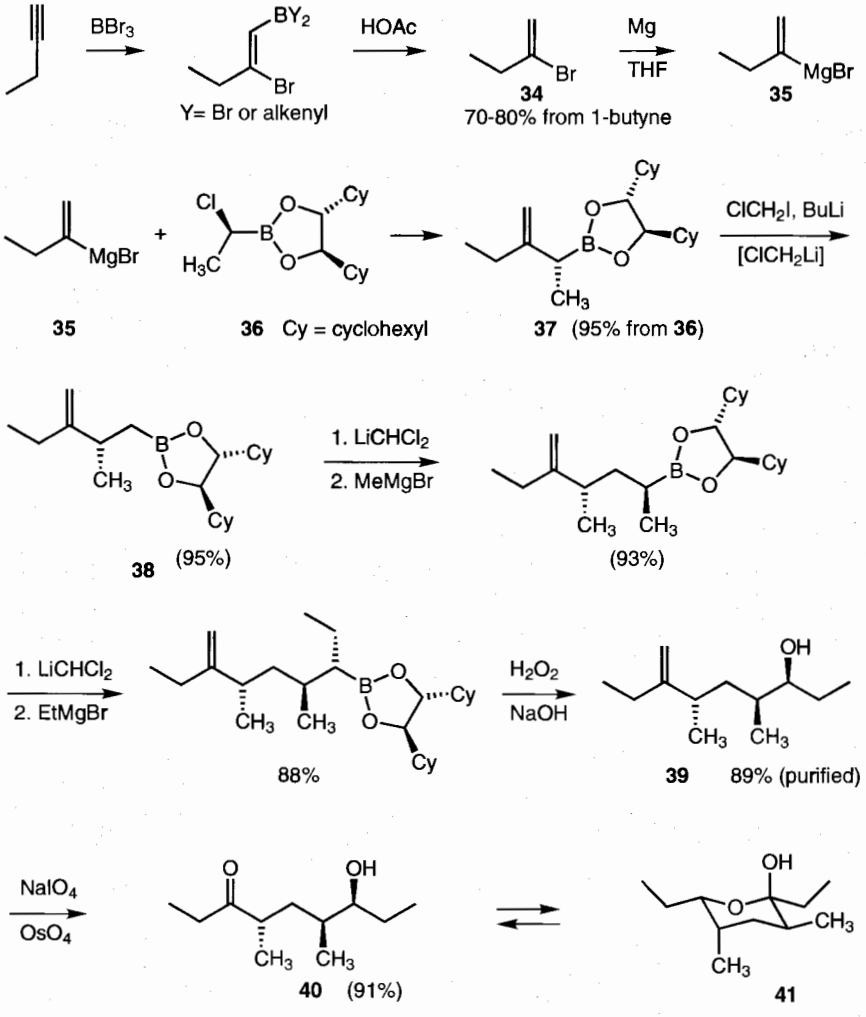
The first route attempted for the synthesis of (3*R*,4*S*)-4-methyl-3-heptanol (**33**, Scheme 8.6) involved cleavage of (*R*,*R*)-2,3-butanediol from the intermediate analogous to **26**, which failed, but cleavage of (*R*,*R*)-2,3-butanediol (1-chlorobutyl)boronate analogous to **25** and esterification with (*S*,*S*)-DIPED was successful. Methylation with methylmagnesium bromide yielded only (*S*,*S*)-DIPED methylboronate (**29**), the first evidence of sequential double diastereoselection and the stereodirected alkoxide migration described above (Scheme 8.2) [13].

Reversal of the order of introduction of the two alkyl groups was then tested. Starting from **29** it was straightforward to prepare DIPED (1-chloroethyl)boronate (**30**) and convert it into the 1-methylbutyl intermediate **31** by treatment with propylmagnesium chloride (Scheme 8.6). (Dichloromethyl)lithium insertion and ethylation readily yielded **32**, which was oxidized to (3*R*,4*S*)-4-methyl-3-heptanol (**33**) (99.8% diastereopurity), which is the trail pheromone of the southeast Asian ponerine ant *Leptogenys diminuta* [13]. The pheromone activity of **33** was 500 times greater than that of any of the other stereoisomers [31].



Scheme 8.6 Synthesis of (3*R*,4*S*)-4-methyl-3-heptanol in high stereopurity. Conditions as in Scheme 8.1, yields (not recorded in literature) similar to Scheme 8.5.

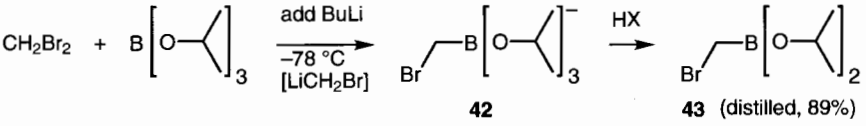
Serricornin (**40**/**41**), the pheromone of the cigarette beetle, *Lasioderma serricorne*, is a more recent synthesis (Scheme 8.7) [32]. The relationship of the two methyl substituted stereocenters requires that the chain be constructed starting from the first of the two methyl groups. (1-Chloroethyl)boronic ester **36** requires substitution by a masked propionyl group, which was introduced via Grignard reagent **35** to form **37**. The required 2-bromo-1-butene (**34**) was obtained via bromoboration of 1-butyne. Insertion of a simple methylene group to form **38** was accomplished with (chloromethyl)lithium generated in situ from chloroiodomethane and butyllithium [33]. The steps from **38** to **39** are straightforward. The methylene group was cleaved to the ketone with sodium periodate and osmium tetroxide to form serricornin (**40**), which equilibrates with its cyclic tautomer **41** (Scheme 8.7).



Scheme 8.7 Synthesis of serricornin (**40**/**41**) in high stereopurity. Conditions for $LiCHCl_2$ reactions as described in Scheme 8.1.

8.3.2
Halogen-substituted Boronic Esters

Simple (halomethyl)boronic esters are not accessible by methods used for higher homologs. The discovery that (chloromethyl)lithium can be generated at –78 °C from chloroiodomethane by treatment with butyllithium in the presence of triisopropyl borate and captured immediately to form the (chloromethyl)borate salt and, after acidification, the boronic ester has provided practical access to these useful reagents [33]. The less expensive reagent dibromomethane under similar conditions generates (bromomethyl)lithium and yields (bromomethyl)(triisopropyl)borate anion (**42**), which is converted into diisopropyl (bromomethyl)boronate (**43**) by treatment with anhydrous hydrogen chloride or, more conveniently, methanesulfonic acid while the reaction mixture is still cold (Scheme 8.8) [34].

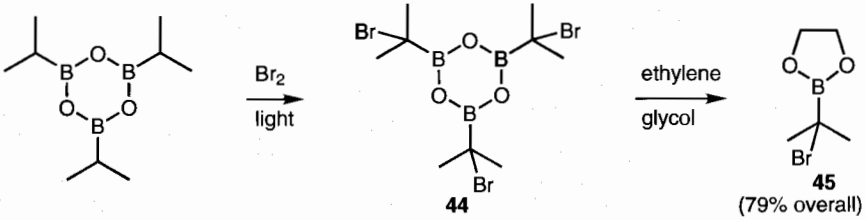


Scheme 8.8 Preparation of diisopropyl(bromomethyl)boronate.

Insertion of a simple CH_2 group into the C–B bond can be accomplished with (chloromethyl)- or (bromomethyl)lithium [33, 34], which works in the same manner as insertion of CHCl with (dihalomethyl)lithium. An example has been illustrated in the serricornin synthesis above (Scheme 8.7).

(α-Chloro-*sec*-alkyl)boronic esters have been made by insertion of (α,α-dichloroethyl)lithium, $LiCCl_2CH_3$, into carbon–boron bonds [35]. Stereocontrol proved weak and unpredictable, and this variant of the (dichloromethyl)lithium reaction does not appear particularly useful.

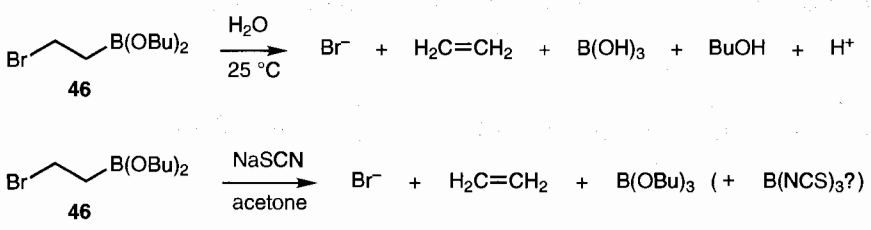
Achiral (α-bromo-*sec*-alkyl)boronic esters are readily accessible via radical bromination of *sec*-alkylboronic esters [36]. Bromination of boronic anhydrides (trialkylboroxines) is much more facile and is a recommended alternative [37]. Dropwise addition of bromine to triisopropylboroxine under fluorescent room lights produced bromo derivative **44** essentially quantitatively (Scheme 8.9). Addition of ethylene glycol produced the boronic ester **45**, which was easily distilled [37].



Scheme 8.9 Bromination of 2,4,6-(triisopropyl)boroxine.

Nucleophilic displacement of α-halogen substituents is facilitated by the boronic ester group, and elimination reactions do not normally occur [9]. This early observation has been substantiated by the large body of chemistry that has accumulated since.

More remote halogen substituents on alkylboronic esters are inert in the reaction with $LiCHCl_2$ if they are separated from the boron atom by three or more carbon atoms, an X–C–C–C–B or longer linkage. However, if the halogen is β to boron, an X–C–C–B linkage, even a weak base will cause rapid elimination of boron and halide, as illustrated by reactions of the simple (2-bromoethyl)boronic ester **46** (Scheme 8.10) [15]. Even the weakly basic thiocyanate ion was sufficient to cause elimination of ethylene (which was confirmed by IR), and iodide ion was the only nucleophile found that would displace bromide from **46** in the usual S_N2 manner. A Grunwald–Winstein plot of the rates of elimination in aqueous ethanol or formic acid indicated strong nucleophilic participation [38]. A linear correlation of log *k* versus pK_b was obtained with a series of substituted anilines $ArNH_2$, but dimethylaniline was slow, suggesting *B–N* coordination. Elimination from a suitably substituted (β-bromoalkyl)-boronic ester with butoxide ion was shown to proceed in a predominantly *anti* manner [38].



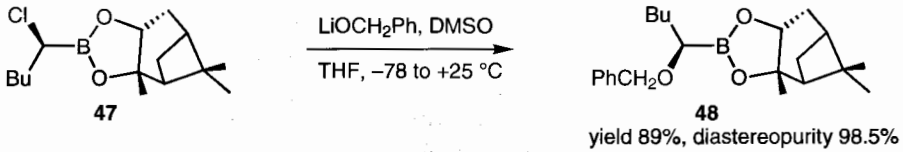
Scheme 8.10 Elimination of ethylene from dibutyl (2-bromoethyl)boronate.

In view of the instability of (β-bromoalkyl)boronic esters in the presence of base, it is not expected that carbon insertion into the C–B bond of an (α-chloroalkyl)boronic ester would yield anything but elimination products. However, pinanediol (α-chlorovinyl)boronate proved resistant enough to β-elimination to allow insertion of a chloromethyl group into the C–B bond [39].

8.3.3
Alkoxy-substituted Boronic Esters

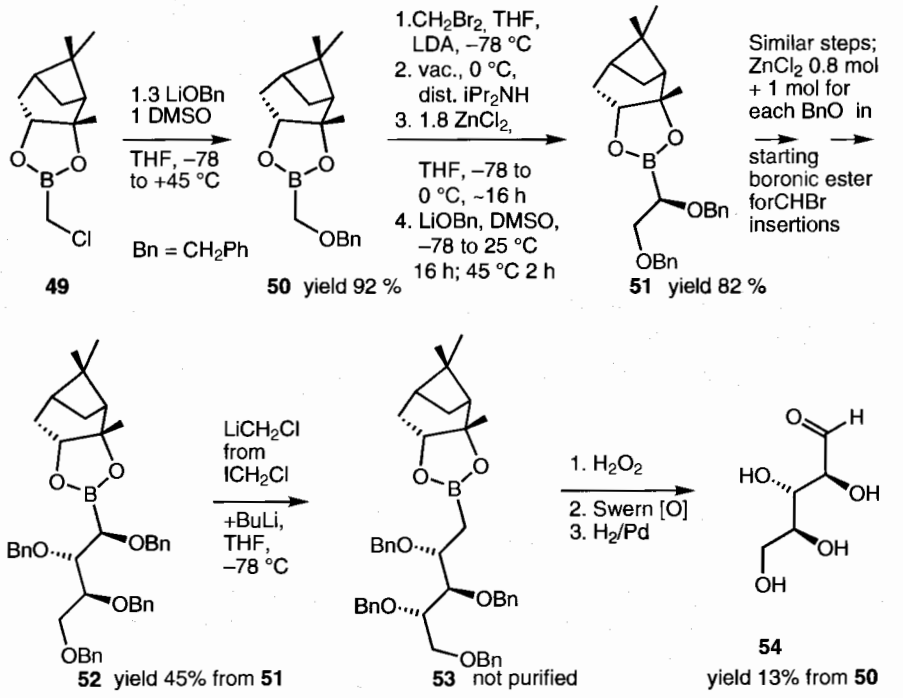
Although B–O bonds are much stronger than B–C bonds and thermodynamics favors boron–oxygen elimination from B–C–C–O linkages to form B–O + C=C, such elimination from (β-alkoxyalkyl)boronic esters is not normally observed unless the compounds are heated above 50–60 °C. This kinetic stability has allowed the synthesis of a wide variety of alkoxy substituted boronic esters. Synthetic targets are usually hydroxy compounds, for which benzyloxy, (*p*-methoxybenzyl)oxy, and trityloxy groups are useful precursors.

(+)-Pinanediol (1*R*)-(1-benzyloxypentyl)boronate (**48**) prepared from chloroboronic ester **47** provided a model for the reaction conditions needed (Scheme 8.11) [29]. Rearrangement of the benzyloxy group from boron to carbon tended to be sluggish, and best results were obtained when about 1 mol of dimethyl sulfoxide was added as a promoter. The reactants are customarily mixed at –78 °C and allowed to warm to room temperature afterward, though there is no evidence that the cold mixing is necessary.



Scheme 8.11 Preparation of (*S*)-pinanediol (*R*)-[1-(benzyloxy)pentyl]boronate.

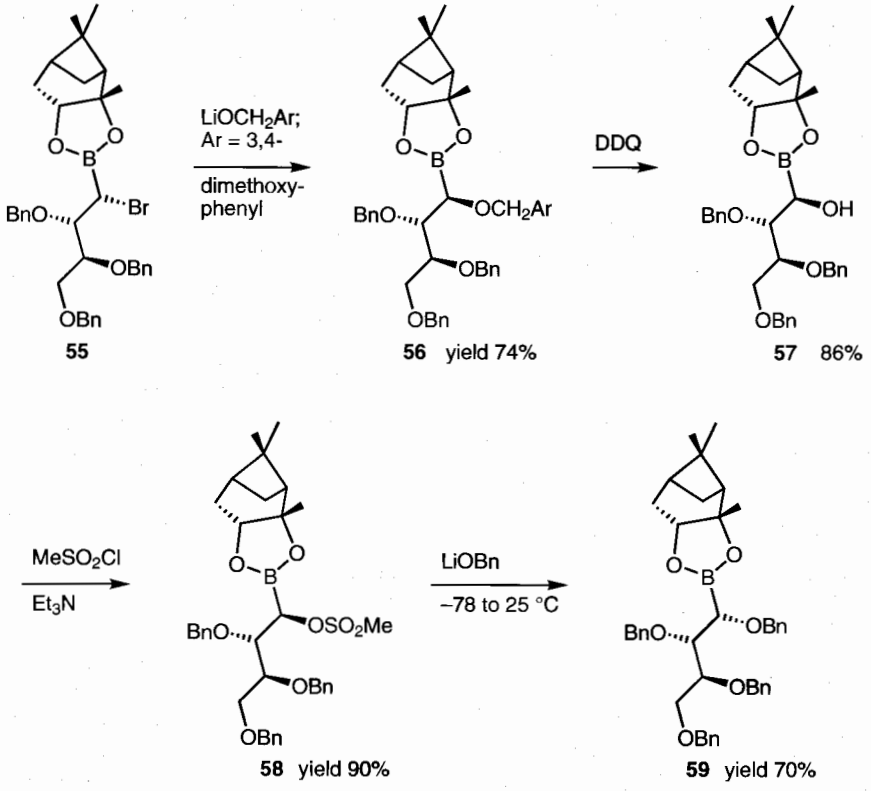
Following the general procedure used for the preparation of **48**, a considerable variety of (alkoxyalkyl)boronic esters have been prepared. Scheme 8.12 illustrates the synthesis of L-ribose [38]. Benzyl oxide substitution on pinanediol (chloromethyl)-boronate (**49**) yielded the benzyloxy derivative **50**. Benzyl oxide substitution in the conversion of **50** into **51** worked best with the bromo intermediate derived from (di-



Scheme 8.12 Synthesis of L-ribose.

bromomethyl)lithium, generated in situ by adding lithium diisopropylamide (LDA) to a mixture of dibromomethane and **50**. For insertion of the CHBr group into **50**, **51**, and the remaining similar chain extensions to **52**, one additional equivalent of zinc chloride was used for each benzyloxy group present, plus the additional equivalent needed to neutralize the diisopropylamine derived from LDA. Although the fifth carbon of L-ribose could be installed with (dichloromethyl)lithium, the yield was poor, and a somewhat more efficient pathway utilized insertion of a simple methylene group into **52** to form **53**. Peroxidic oxidation to the primary alcohol, oxidation to the aldehyde with DMSO and oxalyl chloride under Swern conditions, and debenzylation with hydrogen over palladium completed the synthesis of L-ribose (**54**) [40].

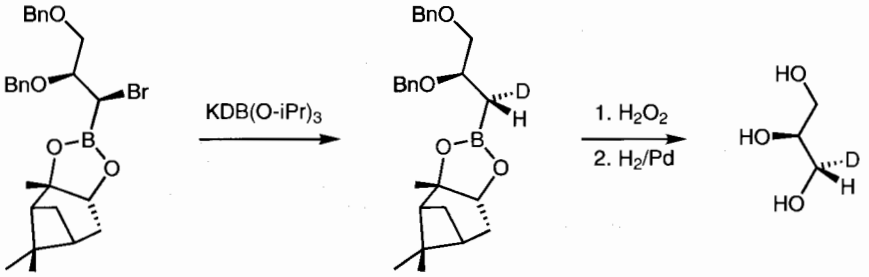
The possibility of double inversion to produce opposite stereochemistry at one stereocenter was also investigated. Conversion of bromo boronic ester **55** (the same precursor used for synthesis of **52**) into the (3,4-dimethoxybenzyl)oxy derivative **56** was straightforward, and dichlorodicyanoquinone (DDQ) oxidation readily yielded the α-hydroxy boronic ester **57**. Conversion of **57** into the methane sulfonate **58** and reaction with lithium benzyl oxide furnished **59**, a diastereomer of **52** (Scheme 8.13) [41].



Scheme 8.13 Double inversion of an (α-bromoalkyl)boronic ester.

The roundabout route to **57** via **56** was required because attempted direct replacement of α-halide by hydroxide or (trimethylsilyl)oxide had failed in a model compound. In view of the instability of (α-aminoalkyl)boronic esters toward deboronation, described in a subsequent section, it is plausible that an (α-hydroxyalkyl)boronic ester might deboronate similarly if the hydroxyl group was deprotonated by base, though (α-hydroxyalkyl)boronic ester **57** and related compounds are stable under neutral or acidic conditions. (Trimethylsilyl)oxide apparently failed because the pinanediol oxygens migrated faster than the silyloxide from boron to carbon [41].

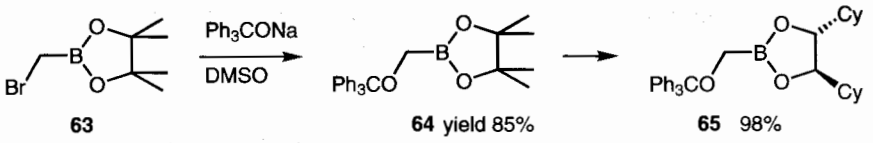
Although the total synthesis of hexoses could not be solved by the foregoing chemistry, a potentially useful route to asymmetrically deuterated glycerol (**62**) was found (Scheme 8.14) [42]. Bromo boronic ester **60**, an intermediate in the L-ribose synthesis, was treated with potassium triisopropoxyborodeuteride to introduce the deuterium label of **61**, which was deboronated and debenzylated to **62**. Enzymatic oxidation of **62** would be expected to yield asymmetrically labeled D-glyceraldehyde, the top hydroxymethyl group being diastereotopically distinguished from the bottom one. Further enzymatic reactions could produce glucose asymmetrically deuterated at C6. By the use of dibromodideuteromethane, deuterated **60** was made and reduced with lithium triethylborohydride to produce the opposite diastereomer of **61** and ultimately **62**, and the other two diastereomers of **62** were prepared from the enantiomer of **60** [42]. Deuterated dibenzyl glyceraldehyde was prepared by using the terminal *p*-methoxybenzyl analog of **60**, which was cleaved with DDQ and oxidized to the aldehyde, but attempted debenzylation was not successful.



60 from **51**, Scheme 8.12, used crude **61** yield 56% from **51** **62** 98%

Scheme 8.14 Synthesis of (1*S*,2*S*)-glycerol-1-*d*. Structures are oriented to preserve the same relation to glucose as Schemes 8.12 and 8.13, with C-6 at the bottom.

Trityloxy is a useful blocking group for terminal hydroxyl. The reaction of lithium or sodium trityloxide with pinacol (bromomethyl)boronate (**63**) proceeds efficiently in anhydrous dimethyl sulfoxide to provide **64**. Transesterification of **64** with (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol ["(*R*)-DICHED"] yields (*R*)-DICHED (trityloxymethyl)boronate (**65**) (Scheme 8.15) [43]. Both **64** and **65** are crystalline and their X-ray structures have been determined. Pinanediol (trityloxymethyl)boronate has been prepared in a similar manner and its X-ray structure determined [43]. These are useful starting points for several synthetic sequences.



Scheme 8.15 Preparation of DICHED [(trityloxy)methyl]-boronate (**65**).

Figure 8.1 illustrates some structures synthesized from **65** or its pinanediol analog. Structure **66** was prepared in an incomplete synthesis directed toward leuconolide [44]. Structure **67** is enantiomeric to the steric relationships of kainic acid [45], and **68** was prepared in an attempted synthesis of kainic acid [46].

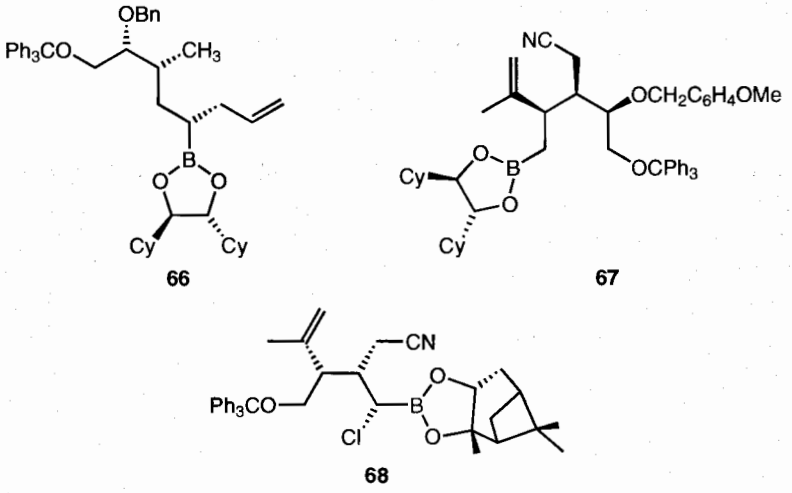
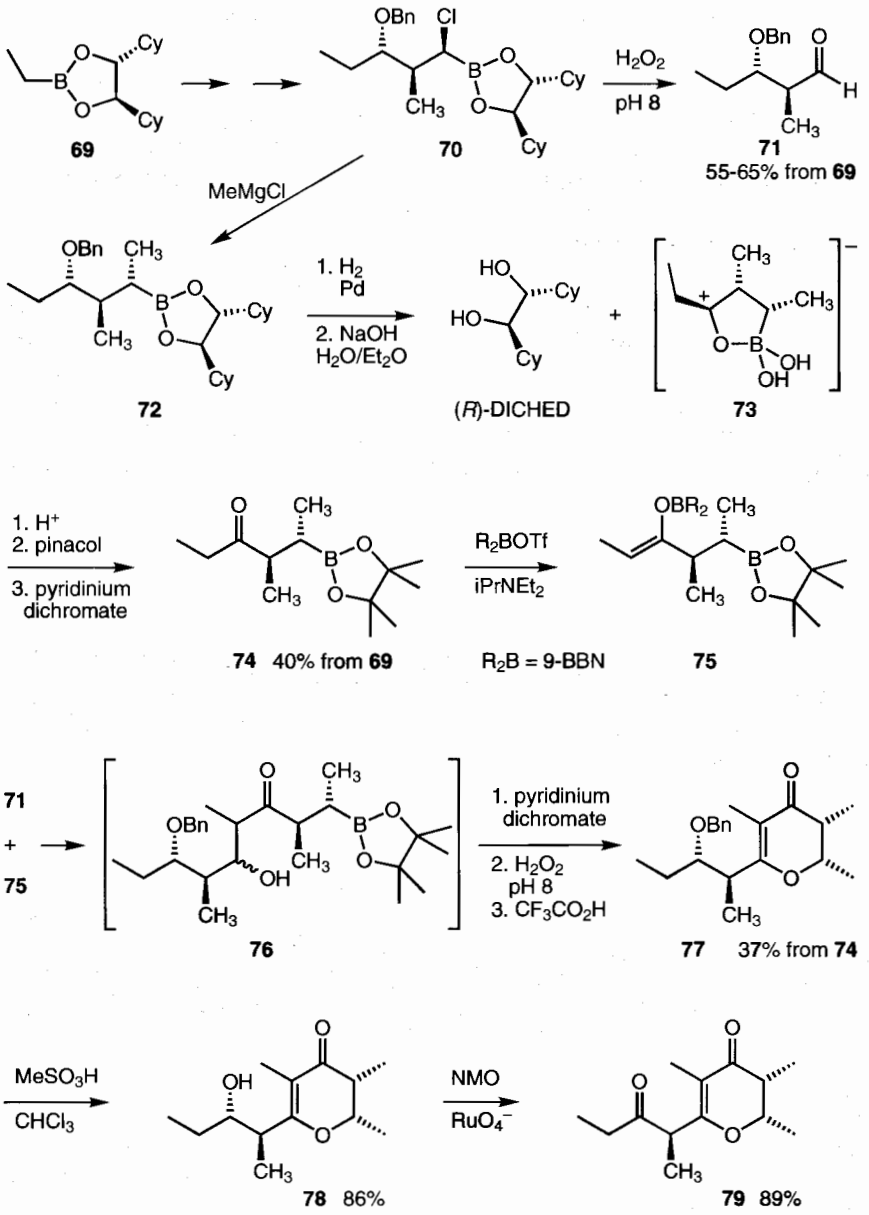


Figure 8.1 Miscellaneous boronic esters containing several stereocenters.

Several syntheses of insect pheromones have involved alkoxy boronic ester intermediates. The lengthy synthesis of stegobinone (**79**) (Scheme 8.16), the aggregation pheromone of the "drugstore beetle," *Stegobium paniceum*, shows the value of ultrahigh diastereoselection [47]. The pheromone is very readily epimerized at the acidic vinylogous diketone site, and as little as 2–3% of epimer cancels the attractant activity. Chain extension of (*R*)-DICHED ethylboronate (**69**) with (dichloromethyl)lithium, conversion of the resulting chloro boronic ester into the benzyloxy derivative, a second chain extension, methylation with a Grignard reagent, and a third chain extension with (dichloromethyl)lithium yielded intermediate **70**, which was used as a common intermediate for both halves of stegobinone in a convergent synthesis. Oxidation of **70** with buffered hydrogen peroxide yielded distilled aldehyde **71** in ~99% stereopurity (~45% yield from **69**, all intermediates used crude). The lability of **71** toward epimerization made diastereomer separation impractical.

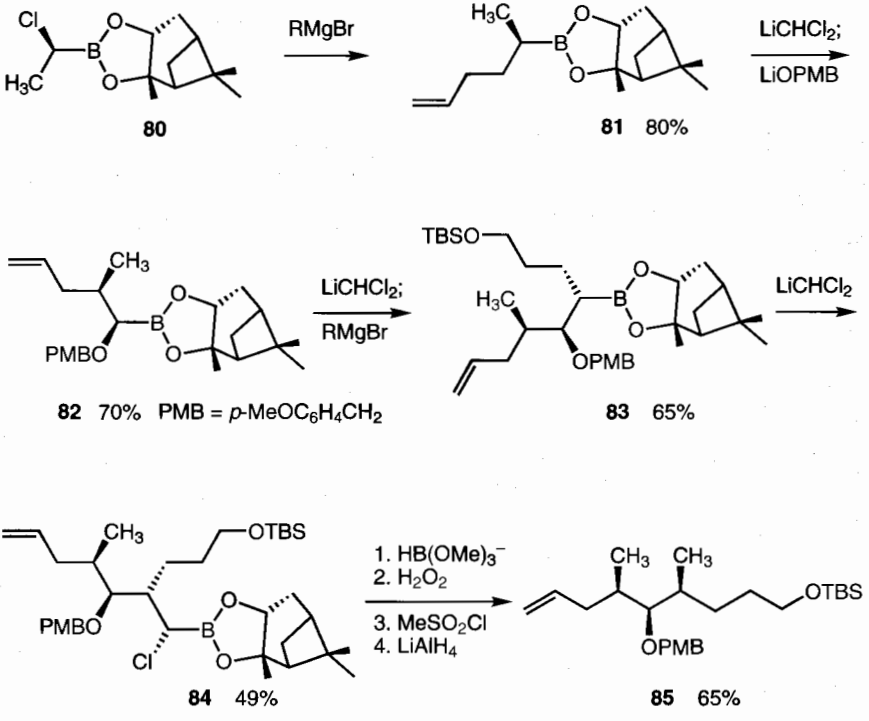


Scheme 8.16 Synthesis of stegobinone (**79**). (Chain extensions with $LiCHCl_2$ were similar to those outlined in Scheme 8.1.)

Methylation of **70** provided **72**, which contains all of the remaining carbon atoms of **79**. Dichromate oxidation of the secondary alcohol from debenzylation of **72** resulted in low yields and partial oxidation of the DICHED. Hydrolysis of **72** to the cyclic borate **73** proved feasible, and oxidation yielded ketone **74** (~35% yield from **69**).

Conversion of **74** into a boron enolate **75** and aldol condensation with **71** to form postulated intermediate **76** was followed by appropriate steps to yield **77**, the first intermediate that was normally purified by chromatography in the sequence. Debenzylation resulted in the first crystalline sample of stegobiol (**78**), a minor component of the natural pheromone. However, tests of pure **78** by Wendell Burkholder showed no attractant activity [48], in contrast to the low activity previously reported for oily natural samples. Perruthenate-catalyzed oxidation of **78** with *N*-methylmorpholine *N*-oxide yielded pure crystalline stegobinone (**79**) having very high attractant activity.

A different interesting application of α-alkoxy boronic esters has been reported by Maurer and Armstrong for the synthesis of the C1–C21 fragment of the serine/threonine phosphatase inhibitor tautomycin [49]. To achieve the correct steric relationships, the synthesis began with preparation and alkylation of (+)-pinanediol (1-chloroethyl)boronate **80** to provide **81** (Scheme 8.17), a route that is analogous to the beginning of the serricornin synthesis from **36** described in Section 8.3.1 (Scheme 8.7). Standard procedures were followed for conversion into the *p*-methoxybenzyl ether **82** and alkylation to **83**. Chain extension to the (α-chloroalkyl)boronic ester **84** for conversion into the second methyl substituent of **85** resulted in some β-elimination of boron and oxygen, which is usually not a problem with (dichloromethyl)lithium reactions. The route to **85** via the (α-chloroalkyl)boronic ester **84** is obsolete and



Scheme 8.17 Intermediates for synthesis of a tautomycin fragment. Conditions for reactions with $LiCHCl_2$ and replacement of chloride for conversion of **80** into **84** are similar to those outlined in Schemes 8.1 and 8.3.

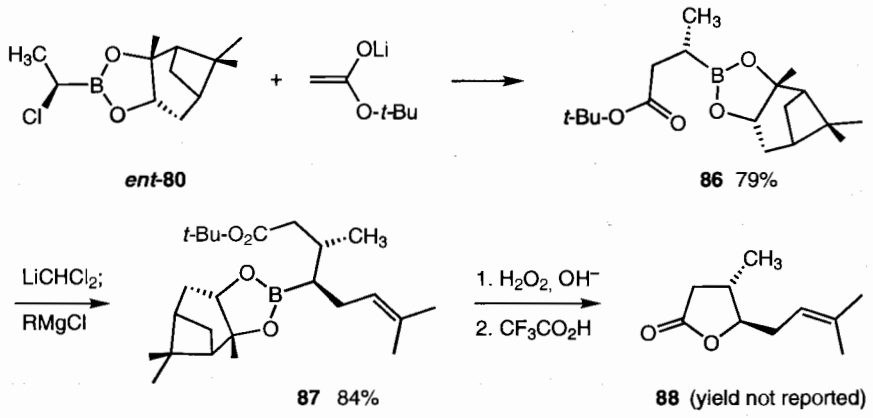
required an extra reduction step to replace chlorine by hydrogen, which could presumably be avoided by using the simple methylene insertion described in Section 8.3.2 [33].

8.3.4
Carbonyl Substituents

Carbonyl substituents on boronic esters normally require two intervening carbons between the carbonyl group and the boronic ester boron. It is not entirely clear why direct acylborane (O=C–B) linkages are unstable. The enol ether of an acetylboronic ester, pinanediol (1-methoxyvinyl)boronate, has been synthesized [39], but it proved too sensitive to allow chloromethyl insertion into the C–B bond [39], and attempts to hydrolyze it to the acetylboronic ester were unproductive.

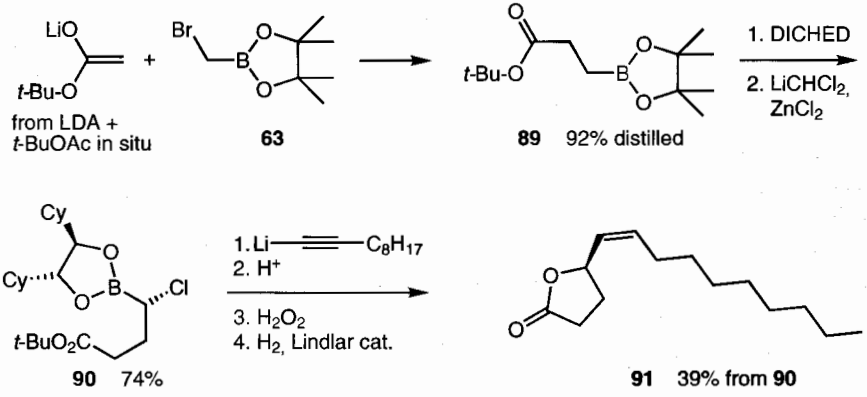
It is not normally possible to make α-boryl substituted carbonyl compounds because the O=C–C–B linkage behaves as an analog of X–C–C–B and elimination occurs, in this case to produce the boron enolate linkage, B–O–C=C [50]. Intramolecular 1,3-migration of boron is a plausible mechanism.

Several boronic esters having a carbonyl substituent with two or more intervening carbons between the boron atom and the carbonyl carbon have been made, and no difficulty has been observed during insertion of a CHCl group with (dichloromethyl)-lithium. An early application was the synthesis of the wing gland pheromone of the African sugar cane borer (**88**) (Scheme 8.18) [29]. (–)-Pinanediol (α-chloroethyl)-boronate (*ent*-**80**, see Scheme 8.17) and *tert*-butyl lithioacetate yielded the β-boryl carboxylic ester **86**, which underwent CHCl insertion and alkylation in the usual manner to form **87**, the immediate precursor to the pheromone (**88**) (Scheme 8.18). The procedure for isolation of **88** was not optimized. After working with essentially nonvolatile pinanediol boronic esters, it is easy to forget that rapidly evaporating a large amount of ether from a small amount of a moderately volatile pheromone may carry away much of the pheromone, just as blowing a stream of air across it would.



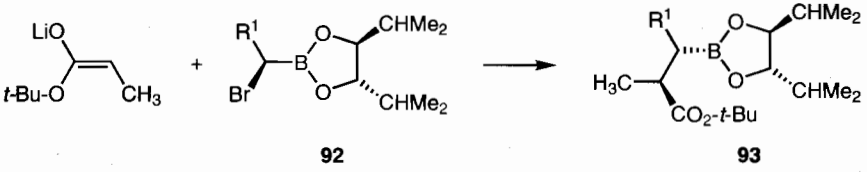
Scheme 8.18 Synthesis of African sugar cane borer pheromone. Conditions for $LiCHCl_2$ reactions and chloride substitutions as described in Schemes 8.1 and 8.3.

tert-Butyl lithioacetate reacts with pinacol (iodomethyl)- or (bromomethyl)boronate to provide the 3-borylpropionate **89** [51, 52]. Conversion into asymmetric α-chloro boronic ester **90** followed by substitution with a lithioalkyne and standard further transformations has provided a short and simple synthesis of the Japanese beetle pheromone (japonilure, **91**) in high stereopurity (Scheme 8.19) [52].



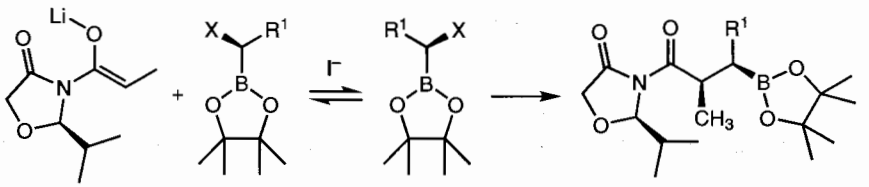
Scheme 8.19 Synthesis of japonilure (**91**).

tert-Butyl lithiopropionate introduces a different type of diastereoselection in synthesis with (α-haloalkyl)boronic esters [20]. Reaction of this enolate with an (*S*)-DIPED (*R*)-(α-bromoalkyl)boronate (**92**) strongly favors formation of the (*S,S*)-diasteromer (threo isomer) of the resulting 2-methyl-3-boryl carboxylic ester **93** (Scheme 8.20). The (*S,S*)/(*R,S*) ratio was 60:1 for R^1 = butyl, 15:1 for R^1 = isopropyl [20]; yields were 59–61% based on the precursor to **92**, $R^1B(O_2C_2H_2iPr_2)$.



Scheme 8.20 Diastereoselective reaction of (α-haloalkyl)boronic esters with an ester enolate.

The initial assumption that the (*E*)-relationship of the methyl substituent and the lithiooxide in the ester enolate controlled the diastereomeric preference proved incorrect. (*R*)-Oxazoline enolate **94**, which has a (*Z*)-relationship between the corresponding substituents similarly strongly favors the (*R,R*)-product (**96**) (Scheme 8.21). Stereoselection is strong enough that from an equilibrating mixture of (α-bromoalkyl)boronic ester enantiomers (**95R/95S**; R^1 = Me, Bu), only the (*S*)-isomer reacts, yielding the (*R,R*)-product (**96**) in 98–99% diastereopurity [53].

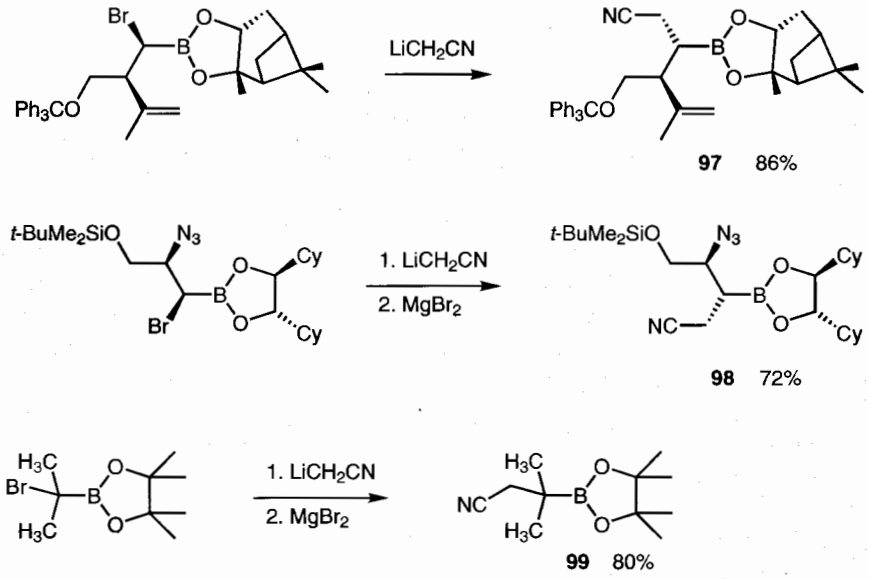


Scheme 8.21 Selective reaction of one enantiomer of an (α-haloalkyl)boronic ester with an asymmetric enolate.

8.3.5
Nitrile Substituents

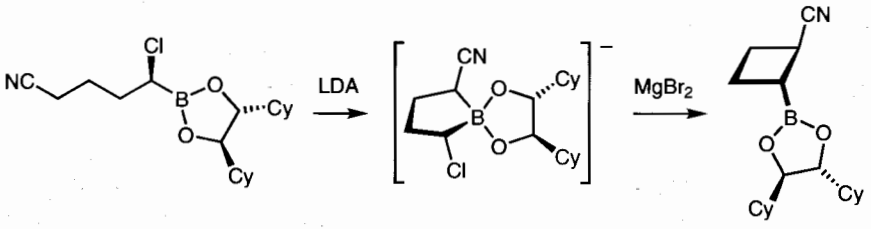
The chemistry of boronic esters that have cyano substituents closely resembles that of boronic esters with carboxylic ester substituents. The same rules apply to the requirements for separation between the boron atom and the substituent. Lithioacetonitrile reacts with (α-haloalkyl)boronic esters in the same manner as does *tert*-butyl lithioacetate, but the less bulky nitrile function encounters fewer steric obstacles. Some examples of sterically hindered compounds that can be made in this way include pinanediol ester **97** [46], (*R*)-DICHED ester **98** [54], and the (α,α-dimethyl-β-cyanoethyl)boronic ester **99** (Scheme 8.22) [37].

A 4-cyano substituted (α-chloroalkyl)boronic ester (**100**) can be cyclized into the corresponding *trans*-2-boryl-1-cyanocyclobutane (**102**) by treatment with LDA (lithi-



Scheme 8.22 Reactions of (α-bromoalkyl)boronic esters with lithioacetonitrile.

um diisopropylamide) followed by addition of magnesium bromide (Scheme 8.23) [55]. The need for the magnesium salt catalyst was discovered after erratic results were obtained with commercial LDA. This LDA originally contained a small amount of magnesium diisopropylamide as a preservative, which enabled the ring closure while the LDA was fresh, but which precipitated with consequent inactivation of the LDA as the sample aged. Zinc chloride was ineffective in promoting the reaction, but anhydrous magnesium bromide solved the problem. The cyclic borate anion **101** probably forms rapidly as soon as the carbon α to the cyano group is deprotonated, but that the subsequent rearrangement step requires a catalyst that is a Lewis acid strong enough to assist removal of the chloride ion but not strong enough to complex with the cyano group and reverse the ring closure.

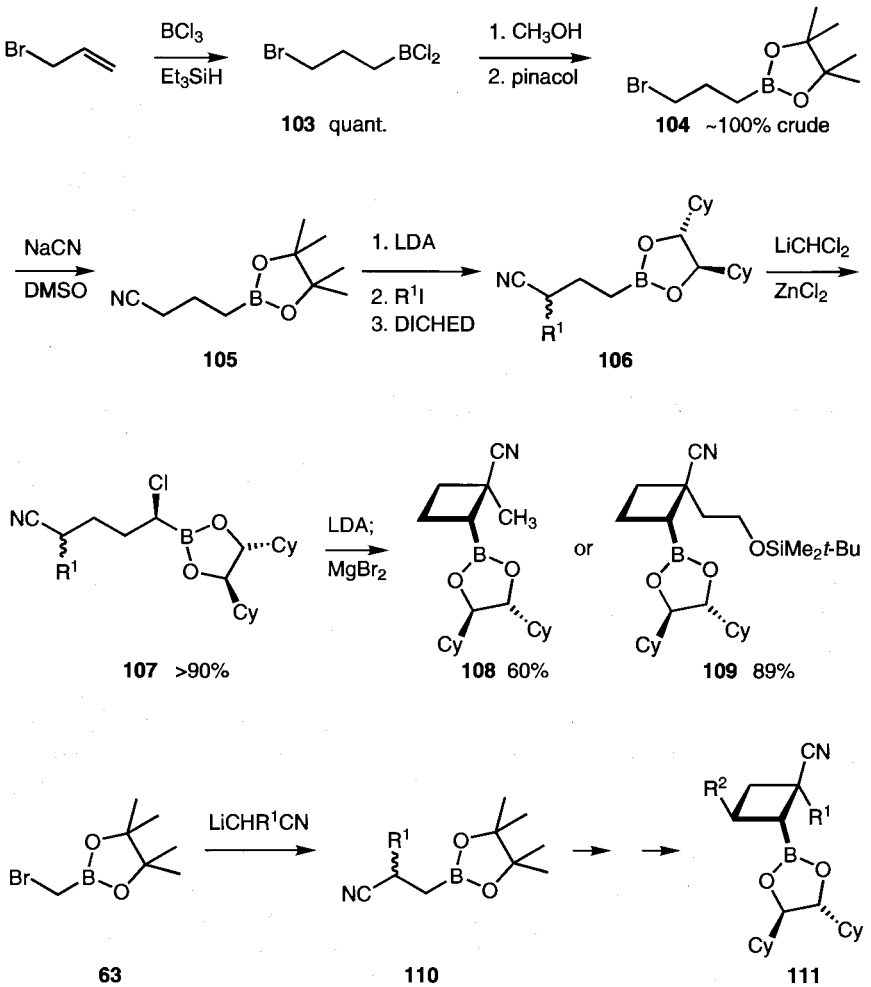


100 **101** **102** 93%

Scheme 8.23 Synthesis of an asymmetric (cyclobutyl)boronic ester.

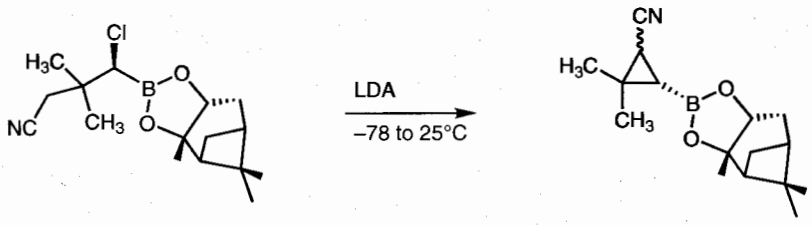
Cyclobutane synthesis allows introduction of substituents on the cyclobutane ring in various patterns (Scheme 8.24) [55]. Allyl bromide with boron trichloride and triethylsilane yields the alkyldichloroborane **103**, which is converted into pinacol (3-bromopropyl)boronate (**104**) and on to the cyano derivative **105** by standard methods. Transesterification of **105** and reaction with $LiCHCl_2$ was used to make **100**. However, **105** can be deprotonated and monoalkylated efficiently, and transesterification then yields **106**. Transesterification with DICHED and asymmetric insertion of the CHCl group furnishes **107**, which cyclizes to **108** or **109** with about the same 20:1 diastereoselection as seen with the unsubstituted intermediate **100**. The pattern of substitution shown by **111** was achieved via reaction of pinacol (bromomethyl)boronate (**63**) with lithioacetonitrile to form **110**, which underwent chain extension and substitution in the usual manner. It was necessary to construct **110** in this way because substitution of a (β-haloalkyl)boronic acid is not possible. With R^1 = H or CH_3, substituents R^2 included Me, Bu, and OBn [55].

Extension of the foregoing chemistry to cyclopropane synthesis was attempted [37]. The problem was complicated by the choice of α,α-dimethyl substituted boronic ester **99** (Scheme 8.22) as a starting point, challenging steric barriers. The corresponding DICHED ester gave poor yields in the chain extension with $LiCHCl_2$, but the pinanediol ester proved satisfactory and furnished intermediate **112** (Scheme 8.25). Ring closure of **112** did not require magnesium bromide as a promoter, but a gross mixture of *trans* and *cis* diastereomers **113** was obtained. More *trans* isomer resulted from shortening the reaction time, suggesting that the diastereomeric mixture re-



Scheme 8.24 Synthesis of di- and trisubstituted (cyclobutyl)boronic esters. Yields of **106** from **104** generally high, not reported in detail. Removal of Et_3SiCl from **104** by distillation was incomplete.

sulted from deprotonation of the relatively acidic cyanocyclopropyl group of 113 under the strongly basic reaction conditions. The possibility of suppressing the isomerization has not been explored.



112 (87% from **99**) **113** 95%

Scheme 8.25 Synthesis of asymmetric (cyclopropyl)boronic esters.

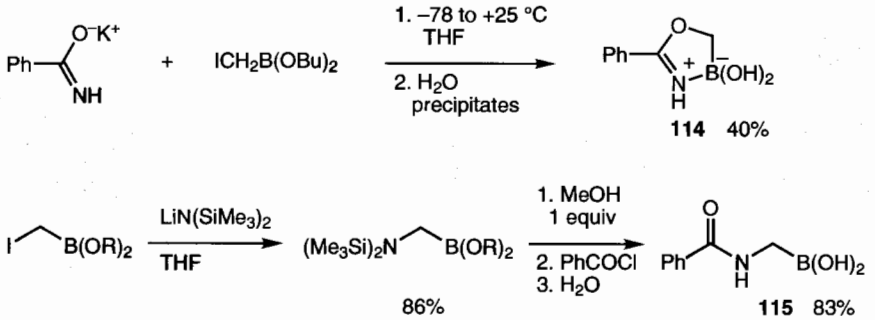
8.3.6
Amino and Amido Substituents

α-Amino boronic acids are of interest as analogs of amino acids, and their acyl derivatives include some significant enzyme inhibitors. The most important of these is the recently marketed anticancer agent bortezomib (Velcade™, Millennium Pharmaceuticals), a proteasome inhibitor that has proved effective for treatment of relapsed and refractory multiple myeloma and is undergoing clinical tests for other activity [56, 57]. Bortezomib is described in more detail at the end of this section.

The first amino substituted boronic esters were tertiary amines derived from dibutyl (iodomethyl)boronate and secondary amines [58]. Mysteriously, ammonia did not yield the simple (aminomethyl)boronic ester, but failure of a reaction does not prove anything. Subsequent rechecking with primary, secondary, and tertiary amines as reactants showed that primary amines with dibutyl (iodomethyl)boronate did not yield isolable primary (aminomethyl)boronic esters [59]. The tertiary amines and quaternary ammonium salts derived from secondary and tertiary amines were stable and easily isolable.

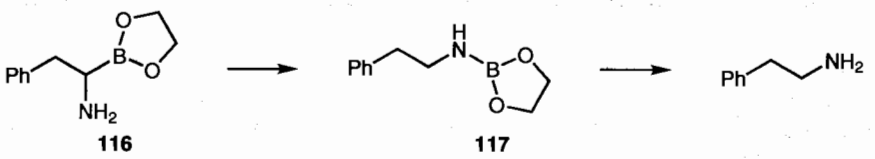
Since (α-acylamidoalkyl)boronic acids were target compounds of primary interest, some effort was put into the possibility of a direct synthesis from (α-chloroalkyl)-boronic esters and metallated amides. A synthesis of (benzamidomethyl)boronic acid from potassiobenzamide and an (iodomethyl)boronic ester was reported, and the compound proved to be an active chymotrypsin inhibitor [60]. However, after a route to true (α-amidoalkyl)boronic esters had been discovered, it was shown that compound **114** isolated from potassiobenzamide substitution had an O–C bond, not an N–C bond (Scheme 8.26) [61]. The route to the N–C bonded isomer **115** is the same as that to other (α-acylamidoalkyl)boronic acids described below in this section. Ironically, the K_i for chymotrypsin binding of the N–C bonded compound **115** was not quite as small as that for the O–C bonded compound **114**, an interesting finding that has not been followed up.

In an unrecorded experiment, D. Majumdar observed that lithio-2,2,6,6-tetramethylpiperidide displaced chloride ion from an (α-chloroalkyl)boronic ester, albeit in mediocre yield. It was then recognized that lithiohexamethyldisilazane, $LiN(SiMe_3)_2$, should provide the requisite primary amino substituent in protected form. This expectation proved correct, and desilylation to the (α-aminoalkyl)boronic acid proved



Scheme 8.26 Preparation of the O- and N-bonded isomer of (benzamidomethyl)boronic acid.

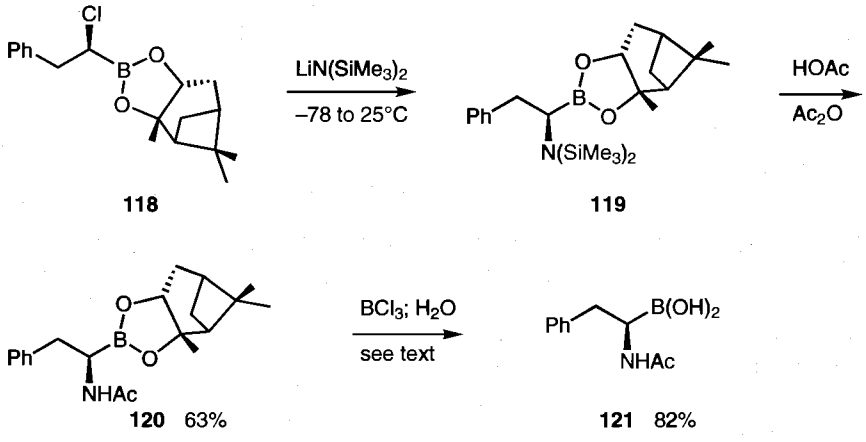
feasible, provided the amino function was promptly protected by acylation or protonation [62, 63]. Free amino boronic esters such as **116** rearranged to the hydrolytically unstable *N*-borylamine (**117**) within a few hours (Scheme 8.27). In the example illustrated, the product isolated was phenylethylamine.



Scheme 8.27 Decomposition of an (α-aminoalkyl)boronic ester.

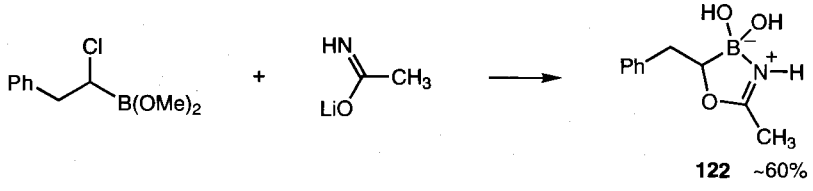
An application that takes advantage of the deboronation is described in Section 8.3.8.

Scheme 8.28 outlines the synthesis of (*R*)-(1-acetamido-2-phenylethyl)boronic acid (**121**), the boronic acid analog of *N*-acetylphenylalanine [62, 63]. (α-Chloroalkyl)-boronic ester **118** was made in the usual way and the reaction with lithiohexamethyldisilazane was carried out under typical conditions for nucleophilic substitution of chloro boronic esters to form silylated amino boronic ester **119**. Desilylation and acylation to **120** were first carried out by adding a mixture of acetic acid and acetic anhydride, though it was soon found that desilylation with one equivalent of methanol yielded an intermediate that could be acylated with benzyloxycarbonyl chloride or other acylating agents [64]. At the time of these reports, the only known way to remove pinanediol from its boronic esters was treatment with boron trichloride, which degraded the pinanediol to black tar and destroyed the carbobenzyloxy substituent, though it left acetamido groups intact. Since then, treatment of pinanediol esters of water-soluble boronic acids with phenylboronic acid in a two-phase diethyl ether–water system has been found to yield pinanediol phenylboronate in diethyl ether and free boronic acid in water [26]. As expected, **121** is a good inhibitor of chymotrypsin, $K_i \sim 2.1$ μM at pH 7.5 [62]. Chymotrypsin was chosen for initial testing because it is a readily available typical serine protease.



Scheme 8.28 Synthesis of the boronic acid analog of *N*-acetylphenylalanine.

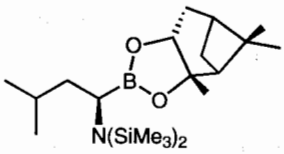
In studies that led to the discovery of a useful route to **121**, the reaction of pinacol (1-chloro-2-phenylethyl)boronate with lithioacetamide was found to yield mostly the *O*-linked isomer **122** (Scheme 8.29) [63]. The yield of precipitated **122** was only about 60%, implying that a major amount of the *N*-bonded isomer (*rac*-**121**) had disappeared into the aqueous phase, which was not examined. Because the *O*-bonded isomer of (benzylamidomethyl)boronic acid was a somewhat stronger inhibitor of chymotrypsin than the *N*-bonded isomer [60, 61], these *O*-bonded isomers should be of biochemical interest, but no additional example has been investigated.



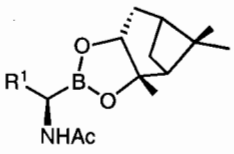
Scheme 8.29 Preparation of the O-bonded isomer of the boronic acid analog of *N*-acetylphenylalanine.

Several additional [α-(bistrimethylsilylamino)alkyl]boronic and derived (α-acetamidoalkyl)boronic esters were synthesized in early work [64, 65]. Pinanediol (*R*)-(bis-1-trimethylsilylamino-3-methylbutyl)boronate (**123**) has subsequently proved to be the most important synthetic intermediate to date of this series for pharmaceutical purposes. Acetamido compounds synthesized are summarized in structure **124** (Figure 8.2).

The free amino boronic acid $CH_3CH(NH_2)B(OH)_2$, an alanine analog, survives for a few hours after its *N*-silylated-*O*-isopropyl protected form contacts water. It is an inhibitor of *Bacillus stearothermophilus* alanine racemase and *Salmonella typhimurium* D-alanine:D-alanine ligase [66].



123

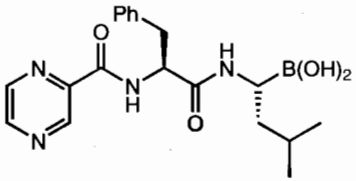


124 R^1 = Me, iPr, iBu, $BnOCH_2$, $Br(CH_2)_3$, $BnO(CH_2)_3$, $MeS(CH_2)_2$

Figure 8.2 Significant silylated and acetylated (α-amidoalkyl)boronic esters.

Once the stability problem with (α-aminoalkyl)boronic esters was understood, several research groups began searching for possible pharmaceutical applications. These studies are covered in Chapter 13.

The only amido boronic acid that has reached the pharmaceutical market to date is Velcade™ (Millennium Pharmaceuticals, bortezomib) (**125**) (Figure 8.3), which received United States FDA approval, May 13, 2003, and approval by the European Union, April 27, 2004, for treatment of relapsed and refractory multiple myeloma and is undergoing clinical tests for other types of cancer [56, 57]. It is an inhibitor of proteasome 26S, and promotes apoptosis in cancer cells that have lost the alternative proteasome. Bortezomib is the first proteasome inhibitor as well as the first boron compound to pass clinical tests and become an approved drug.



125

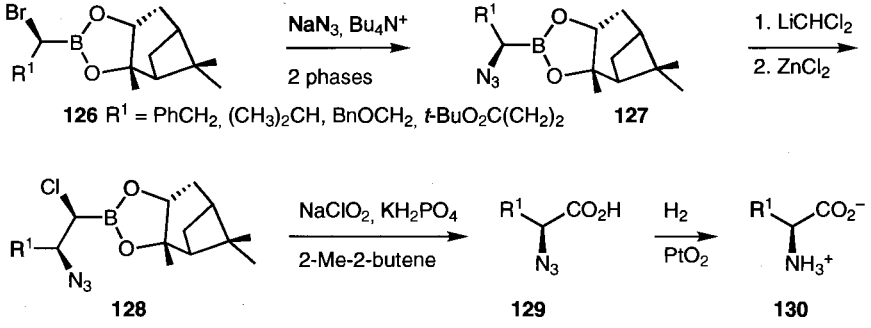
Figure 8.3 Velcade™ (bortezomib).

8.3.7
Azido Substituents

The stability of α-azido substituents in boronic esters was first observed in exploratory studies [29]. Azido groups are compatible with several standard reactions of boronic esters, including chain extension with (dichloromethyl)lithium and substitution of the resulting α-chloro substituent. After peroxidic deboronation, reduction of the azido group with lithium aluminum hydride led to an asymmetric amino alcohol, (5*S*,6*S*)-$BuCH(NH_2)CH(OH)Bu$, in 98% diastereopurity [29]. Details of a more recent amino alcohol synthesis are shown below in Scheme 8.31.

Once this information had been obtained, a simple asymmetric synthesis of amino acids (**130**) followed (Scheme 8.30) [67]. Reactions with azide ion were sluggish, and (α-bromoalkyl)boronic esters (**126**) were preferred. These reactions were carried out

in a two-phase system, dichloromethane–water, but because dichloromethane reacts slowly with azide ion to form explosive diazidomethane, the use of ethyl acetate for the organic phase is strongly recommended [54]. Because azide ion differs little from halide ions in nucleophilicity, a large excess of sodium azide was needed to avoid epimerization. Chain extension of (α-azidoalkyl)boronic esters **127** into **128** was routine, and oxidation with sodium chlorite produced the azido acids **129**. Reduction to the amino acids **130** was straightforward, and standard deprotection steps followed to prepare serine or glutamic acid.



126 R^1 = $PhCH_2$, $(CH_3)_2CH$, $BnOCH_2$, t-$BuO_2C(CH_2)_2$ **127**

128 **129** **130**

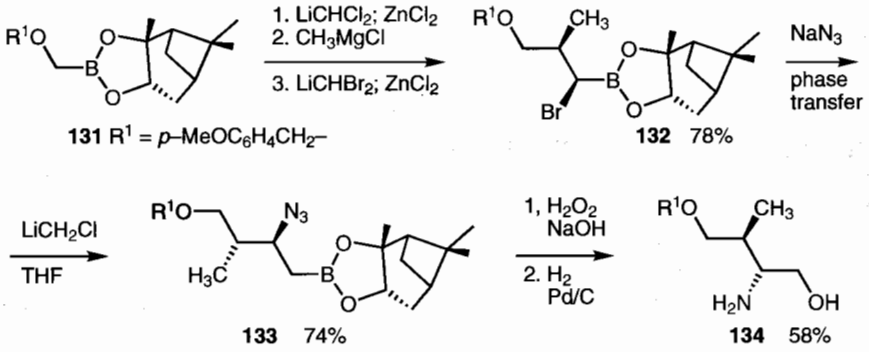
Yields of **130** from **126**: R^1 = $PhCH_2$ 63%, $(CH_3)_2CH$ 57%, $HOCH_2$ 39%, $HO_2C(CH_2)_2$ 32%

Scheme 8.30 Synthesis of amino acids. Deprotection of R^1: $BnOCH_2$ to $HOCH_2$, Pd catalyst used for conversion of **129** into **130**; t-$BuO_2C(CH_2)_2$, **129** treated with CF_3CO_2H before reduction to **130**.

A simple extension of the foregoing synthesis was also shown to be useful for making phenylalanine asymmetrically deuterated in the CHD group [68]. Azido substituted boronic esters have been mentioned in passing in Section 8.3.5 in conjunction with another synthesis (Scheme 8.22) [54].

A useful application of this chemistry has been reported for the preparation of an intermediate amino alcohol (**134**) used in the total synthesis of the phosphatase inhibitor motuporin (Scheme 8.31) [69]. Straightforward chain extensions of (*R*)-pinanediol (*p*-methoxybenzyloxymethyl)boronate (**131**) to (α-bromoalkyl)boronic ester **132** followed by azide substitution furnished (α-azidoalkyl)boronic ester **133**, which was converted into **134** by chain extension with $LiCH_2Cl$ followed by the usual peroxidic deboronation and azide reduction.

The azido group is inert to boronic esters but reacts readily with alkyldichloroboranes [70]. Section 8.4.1 describes the conversion of boronic esters into (alkyldichloro)boranes and their reaction with azides.



131 R^1 = *p*–$MeOC_6H_4CH_2$–

132 78%

133 74%

134 58%

Scheme 8.31 Synthesis of an asymmetric amino alcohol via the azide.

8.3.8
Other Applications of (α-Haloalkyl)boronic Esters

The instability of (α-aminoalkyl)boronic esters having a free NH group has been taken advantage of in the use of pinacol (chloromethyl)boronate, $ClCH_2B(O_2C_2Me_4)$, to achieve monomethylation of primary amino groups of resin-bound amino acids [71]. When the reaction is run in dimethylformamide containing a small amount of *tert*-amyl alcohol, the boron mostly remains bound to the amine nitrogen as $RN(Me)B(O_2C_2Me_4)$ and prevents further alkylation. In the small percentage of product in which a second molecule of pinacol (chloromethyl)boronate adds to the nitrogen, the product $RN(Me)CH_2B(O_2C_2Me_4)$ does not deboronate, and hydrogen peroxide treatment of the resin-bound material removes the CH_2 group as formaldehyde, leaving RNHMe as the product. This process for making pure secondary alkylmethylamines has not been investigated in other contexts.

Asymmetric boronic esters synthesized by hydroboration chemistry have been converted into asymmetric carboxylic acid derivatives having carboxyl carbon in place of the boron atom via homologation with (dichloromethyl)lithium and oxidation [7]. This sequence is relatively inefficient because of the several steps required. If the asymmetric boronic ester is generated via catalytic hydroboration with catecholborane, the homologation process is a more efficient way of introducing the carboxyl carbon [72].

8.4
Other Aspects of (α-Chloroalkyl)boronic Ester Chemistry

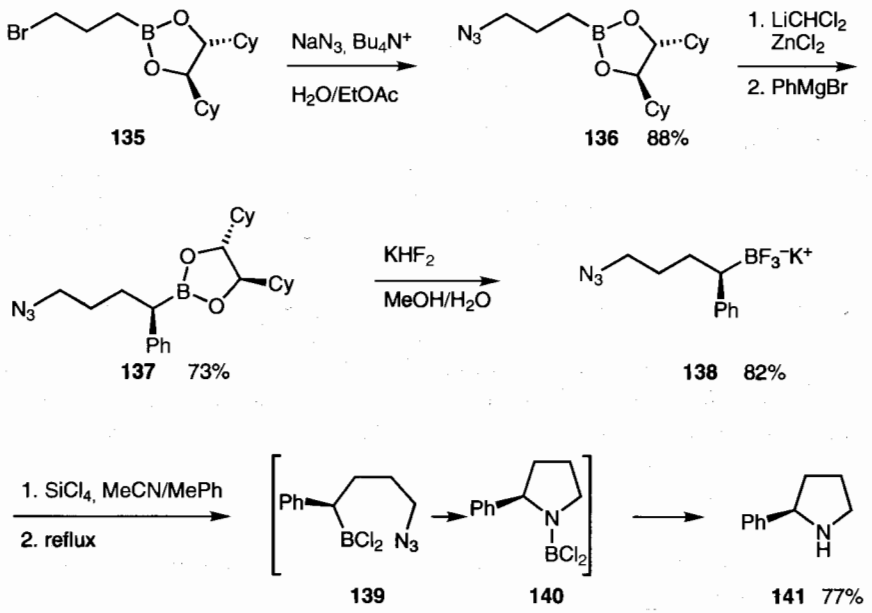
8.4.1
Replacement of Boronic Ester Groups

One of the limitations of (α-chloroalkyl)boronic ester chemistry has been that the chiral directors are difficult to cleave from boron, and boronic esters are inert in some of the useful transformations of trialkylboranes and alkyldihaloboranes. The vigorous conditions that will remove pinanediol from any pinanediol boronic ester, treatment with boron trichloride [12], leave the pinanediol as tarry ruins and with it any sensitive functionality on the boronic ester. The much milder cleavage by transfer of pinanediol or other chiral diol to phenylboronic acid in a two-phase system works well if the boronic acid to be isolated is water soluble [26]. Other cleavage methods include reduction of pinanediol boronic esters with lithium aluminum hydride or alkylation to borinic ester intermediates [73].

Mild methods were known in some other specific instances. The (*R*,*R*)-2,3-butanediol ester of (1-chloro-2-methylpropyl)boronic acid with diethanolamine yielded the crystalline diethanolamine ester [13]. DICHED (α-benzyloxyalkyl)boronates have been cleaved with TAPS buffer [a water-soluble *gem*-tris(hydroxymethyl) compound] and excess base [74]. However, these methods were inefficient and not general.

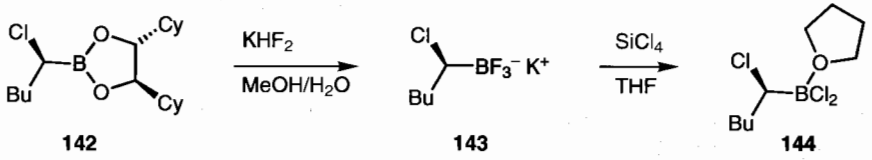
The discovery that reaction of thionyl chloride and imidazole could cleave DICHED boronic esters efficiently to amine haloborane derivatives in the presence of crushed borosilicate glass at first appeared to provide a promising route [75]. The requirement for borosilicate glass surface was unexpected and interesting, but efficient as the recovery of free DICHED via its cyclic sulfite ester was, hydrolysis of the bis(imidazolyl)(alkyl)chloroboronium chlorides proved sluggish and incomplete. Vedejs and co-workers had reported conversion of arylboronic acids into aryltrifluoroborate salts with potassium bifluoride [76], and this reaction proved feasible not only with boronic acids but also with chiral boronic esters, including pinanediol esters [77].

The first application of the alkyltrifluoroborate salts was the conversion into alkyldihaloboranes by silyl halides and subsequent reaction with alkyl azides [77]. An example of a useful synthesis was the preparation of (*S*)-2-phenylpyrrolidine (**141**) (Scheme 8.32). (*S*)-DICHED (3-bromopropyl)boronate (**135**) was converted into the 3-azido derivative **136** at reflux temperature under phase-transfer conditions. The usual reaction with (dichloromethyl)lithium followed by phenylmagnesium bromide to form DICHED ester **137** was followed by treatment with potassium bifluoride in aqueous methanol to provide the alkyltrifluoroborate salt **138**. Neither boronic esters nor alkyltrifluoroborate salts react with alkyl azides. Reaction of **138** with trimethylsilyl chloride yielded (*S*)-2-phenylpyrrolidine (**141**), but reaction with silicon tetrachloride proved much faster and more efficient. At first it was thought that the intermediates **139** and **140** were probably difluoroboranes in accord with literature precedent [76], but careful reinvestigation has revealed that reaction of alkyltrifluoroborate salts with silicon tetrachloride in coordinating solvents yields alkyldichloroboranes [78].

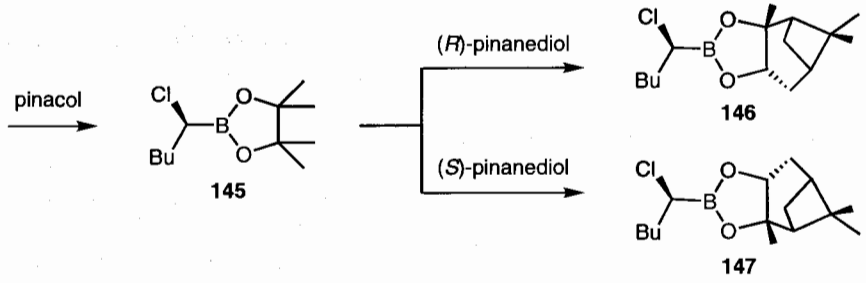


Scheme 8.32 Synthesis of (*R*)-2-phenylpyrrolidine (**141**).

The reaction of (α-chloroalkyl)boronic esters with silicon tetrachloride does not epimerize (α-chloroalkyl)boron groups. As a test, (*S*)-DICHED (1-chloropentyl)-boronate (**142**) with potassium bifluoride was converted into potassium (1-chloropentyl)trifluoroborate (**143**), which was treated with silicon tetrachloride in THF to form (1-chloropentyl)dichloroborane (**144**). The dichloroborane was converted into the stable pinacol ester **145**, which was transesterified to the (*R*)- and (*S*)-pinanediol esters **146** and **147**, respectively (Scheme 8.33). ^{1}H NMR spectra of these two diastereomers differ sufficiently to show that each was pure and free from more than 1–2% of the other. Compound **144** was shown to react readily with diethylzinc followed by base and finally hydrogen peroxide to yield the expected (*S*)-3-heptanol, but this chemistry awaits further development to achieve efficient synthetic procedures.



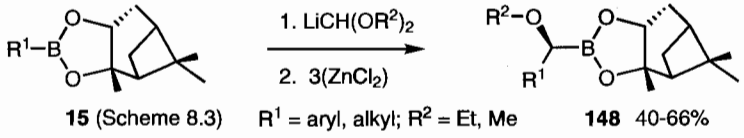
Scheme 8.33 Conversion of a DICHED (α-chloroalkyl)boronic ester into an (α-chloroalkyl)dichloroborane without loss of stereopurity. Yields for these transformations, though generally good, were not optimized and were not reported.



Scheme 8.33 Continued

8.4.2
Chain Extension with (Dialkoxymethyl)lithium

An interesting new approach to (α-alkoxyalkyl)boronic esters bypasses (α-chloroalkyl)boronic esters and utilizes direct insertion of (dialkoxymethyl)lithium into the C–B bond of an (*S*)-pinanediol alkylboronate (**15**) (Scheme 8.34) [79]. The (dialkoxymethyl)lithiums were prepared from the corresponding (dialkoxymethyl)-trimethyltins with butyllithium at –100 °C. The resulting (*S*)-(α-alkoxyalkyl)boronic esters **148** have the same relative configuration as (*S*)-(α-chloroalkyl)boronic esters produced in an analogous manner from the reaction of **15** with (dichloromethyl)lithium, opposite the (*R*)-configuration that would be obtained from alkoxide substitution on the corresponding (*S*)-α-chloro compound. Diastereomeric ratios reported for R^1 = aryl or secondary alkyl were excellent, but primary alkyl groups gave only ~5:1 ratios. Yields were in the 40–66% range. Unfortunately, attempts to prepare (dibenzyloxy)methyllithium (R^2 = benzyl) failed, and the reaction is so far limited to R^2 = methyl or ethyl.

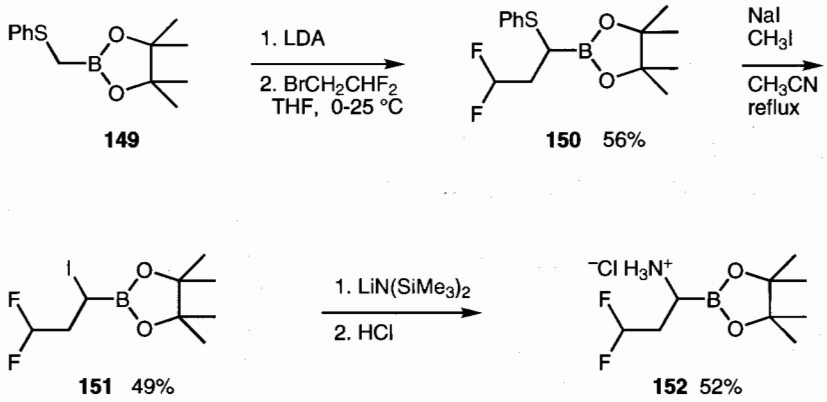


Scheme 8.34 Conversion of boronic esters into (α-alkoxyalkyl)-boronic esters with (dialkoxymethyl)lithium.

8.4.3
(α-Iodoalkyl)boronic Esters via (Phenylthiomethyl)boronic Esters

An older route to (α-iodoalkyl)boronic esters involved preparation of pinacol (phenylthiomethyl)boronate (**149**), which could be deprotonated and the resulting anion alkylated by alkyl halides [80]. The phenylthio group can be replaced with iodo by treatment with methyl iodide and sodium iodide in acetonitrile. This route can only yield racemic (α-iodoalkyl)boronic esters, but it has been revived for preparation of

some (α-amidoalkyl)boronic acids that are inaccessible via the (dichloromethyl)lithium reaction because of unstable precursors [81]. An example is the preparation of (phenylthio)boronic ester **150**, which was converted into the iodo derivative **151** with sodium iodide and methyl iodide in refluxing acetonitrile (Scheme 8.35). The amine salt **152** was obtained via the usual reaction with lithiohexamethyldisilazane followed by acid hydrolysis. The amine was acylated in the usual way (Section 8.3.6), and separation of diastereomers was aided by transesterification to pinanediol esters [81].



Scheme 8.35 Preparation of a fluorinated (α-aminoalkyl)boronic ester.

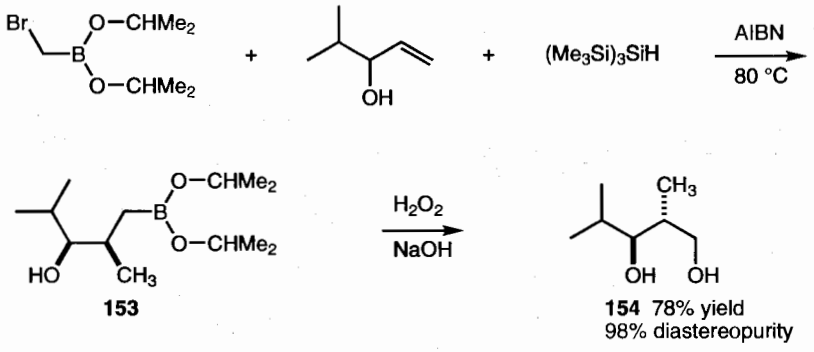
8.4.4
Free Radicals from (α-Haloalkyl)boronic Esters

Free radical chemistry is not generally a useful way to introduce asymmetry, and this review is very brief. However, some examples of high diastereoselectivity have been found. There is substantial evidence that α-boryl radicals are stabilized by π-bonding involving the vacant p-orbital of boron [82].

Free radical additions to alkenylboronic esters provided the first access to (α-haloalkyl)boronic esters [8]. Intramolecular cyclizations involving radical additions to alkenylboronic esters have been reported and, also, a (1-iodo-5-hexenyl)boronic ester cyclizes to the cyclopentyl derivative under radical conditions [83]. Reaction of pinacol (1-iodopentyl)boronate with tributyltin hydride and butyl vinyl ether yielded the addition product pinacol (1-butoxy-3-heptyl)boronate (71%), but addition of the borylalkyl radical to methyl acrylate was inefficient and yielded mainly the simple reduction product, pinacol pentylboronate [84].

Intermolecular radical additions are facilitated if the alkene has a hydroxyl substituent that can form an ester to boron, so that the actual addition is intramolecular. Accordingly, bis(2-bromoethyl) alkenylboronates readily cyclize under radical conditions [85]. This concept was quickly extended to α-boryl radicals [86]. One of the more favorable examples is the reaction of diisopropyl (bromomethyl)boronate with 4-methylhex-1-en-3-ol and tris(trimethylsilyl)silane in the presence of azobis(isobuty-

ronitrile) (AIBN) in refluxing benzene. Ligand interchange would produce a substantial proportion of esterified 4-methylhex-1-en-3-ol. The reaction produced the postulated boronic ester intermediate **153** and, finally, its oxidation product **154** in 78% isolated yield and 98% diastereomeric purity (Scheme 8.36) [86]. However, less hindered substituents than isopropyl resulted in much lower diastereoselectivity.

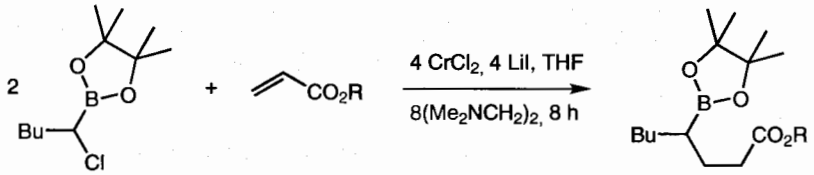


153

154 78% yield
98% diastereopurity

Scheme 8.36 Diastereoselective reaction of diisopropyl(bromomethyl)boronate with an allylic alcohol and a silane under free radical conditions.

(α-Chloroalkyl)boronic ester (**155**) reacts with chromous chloride and an acrylate ester in the presence of lithium iodide and TMEDA to form **156**, providing another useful example of an α-boryl radical reaction (Scheme 8.37) [87].



155

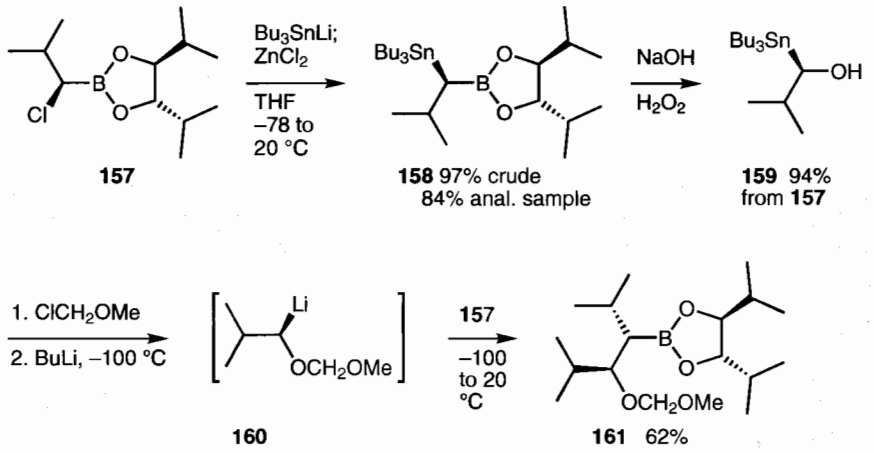
R = $(CH_2)_3Ph$

156 yield 92%

Scheme 8.37 Radical addition of an (α-chloroalkyl)boronic ester to an acrylate ester.

8.4.5
Metal Substitutions of (α-Haloalkyl)boronic Esters

Several types of replacement of halide by metals are known. The only one that appears to have direct utility in asymmetric synthesis is the reaction of (tributylstannyl)lithium with (α-chloroalkyl)boronic esters. The replacement is stereospecific and provides a route to α-lithioethers having high enantiopurity [88]. This chemistry is illustrated by the conversion of (*S*)-DIPED (*R*)-(1-chloro-2-methylpropyl)boronate (**157**) into the (*S*)-tributylstannyl derivative **158** (Scheme 8.38). The displacement is unusually sluggish and was promoted with zinc chloride. Peroxidic deboronation yielded



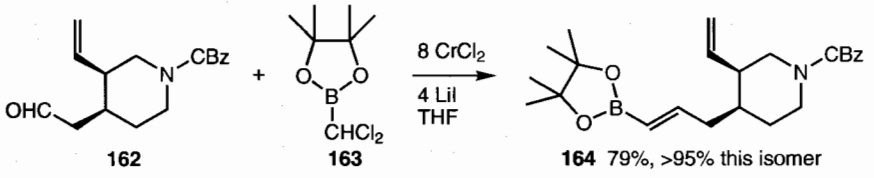
Scheme 8.38 Preparation and use of an asymmetric α-lithioalkyl ether (**160**).

the tin-substituted alcohol **159**, which was converted into the methoxymethyl ether and treated with butyllithium at –100 °C to form the lithio ether **160**. Addition of the (α-chloroalkyl)boronic ester **157** led to the coupled product **161** [88].

Pinacol (iodomethyl)boronate reacts with activated zinc to produce the synthetically useful zinc substituted boronic ester $IZnCH_2B(O_2C_2Me_4)$ [89]. Several pinacol (α-bromoalkyl)boronates have also been converted into the zinc derivatives. These can be activated with copper salts and coupled with various electrophiles.

A dichromium derivative has been prepared from pinacol (dichloromethyl)-boronate (**163**), anhydrous chromous chloride, and lithium iodide in THF at 25 °C [90]. With various aldehydes, RCHO, this reagent adds to the carbonyl carbon to form *trans*-1-alkenylboronic esters, $RCH{=}CH{-}B(O_2C_2Me_4)$. For most examples yields were 84–91%, *E*:*Z* ratios >95:5. This reaction was used recently to convert aldehyde **162** into alkenylboronic ester **164**, an intermediate used for a Suzuki–Miyaura coupling in the asymmetric total synthesis of quinine and quinidine (Scheme 8.39) [91]. In the modified procedure, the chromium reagent was generated from **163** in the presence of the aldehyde substrate.

A *gem*-bis(bromozinc) reagent, $(BrZn)_2CHB(O_2C_2Me_4)$, has been prepared from pinacol (dibromomethyl)boronate and zinc metal in the presence of a lead catalyst [92]. This reagent reacts with aldehydes in the presence of titanium tetrachloride to



Scheme 8.39 Reaction of a (dichloromethyl)boronic ester with chromium(II) chloride.

produce mainly *trans*-1-alkenylboronic esters, though the *E*:*Z* ratios appear to be lower than with the corresponding chromium reagent. The zinc reagent can be coupled catalytically with aryl or allyl halides to provide the corresponding disubstituted methylboronic esters, and the coupling can be done in a controlled stepwise manner.

8.5 Conclusion

The utility of (α-haloalkyl)boronic esters as reagents for asymmetric synthesis is well established. A wide variety of products can be made in high stereopurity. This fundamental research has been supported for many years by the National Science Foundation, with periods of additional support from the National Institutes of Health. The discovery of the useful anticancer pharmaceutical Velcade™, which is derived from an (α-aminoalkyl)boronic ester made from an (α-haloalkyl)boronic ester, provides an example of the practical long-range benefits of support for fundamental research.

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9
Cycloadditions and Other Additions to Alkenyl-, Alkynyl- and Dienyl Boronic Esters

Bertrand Carboni and François Carreaux

A wide variety of reactions involving additions to unsaturated boronic esters have become known since the pioneering works of D. S. Matteson in the early 1960s [1]. Unlike their organometallic analogues, alkenyl- and dienyl boronates are stable to air and moisture, mostly as hindered cyclic diol derivatives, and are easy to purify by column chromatography or distillation. Alkynyl derivatives are much more sensitive to hydrolysis, but can be manipulated quite easily provided appropriate precautions are used. Besides the palladium-catalyzed cross-coupling reactions, which certainly remain one of the most important tools of organoborane chemistry, other attractive reactions involving the formation of one or two new carbon–carbon or carbon–heteroatom bonds have found valuable applications in organic synthesis. The present chapter reviews significant and recent advances in this attractive area of organoboron chemistry.

9.1
Ionic Addition

9.1.1
Halogenation and Hydrohalogenation

Bromination of dibutyl vinylboronate at low temperature readily affords a stable dibromo derivative [2, 3]. Similarly, (*E*)-alkenylboronic acids or their catechol esters yield the corresponding substituted compound by stereospecific *trans* addition of bromine. Treatment with base induced *anti* elimination of the boronic group and the bromine ion. The final result of this sequence was the replacement of boron by bromine with inversion of olefin geometry in excellent yields and 99% stereochemical purities (Scheme 9.1) [4].

(*E*)-1-Alkenylboronic acids also add chlorine and iodine to produce intermediates that, upon treatment with a base, provide the corresponding (*Z*)-1-halogenoalkenes. When sodium hydroxide was added prior to the addition of iodine, iodination pro-

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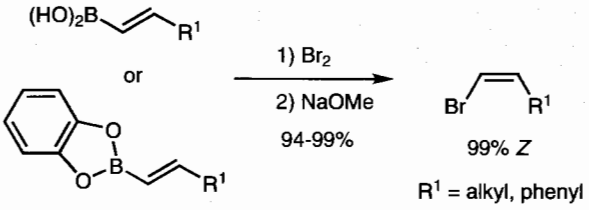
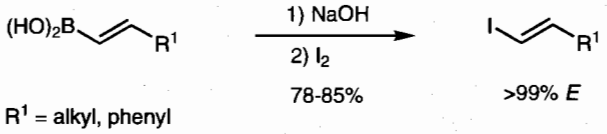


Scheme 9.1 Bromination of alkenylboronic acids and esters.

ceeded with retention of configuration (Scheme 9.2) [5]. Direct radioiodination of (*Z*)-vinylboronic acid esters to the corresponding vinyl iodides using $Na^{123}I$ and chloramine-T has been described [6].

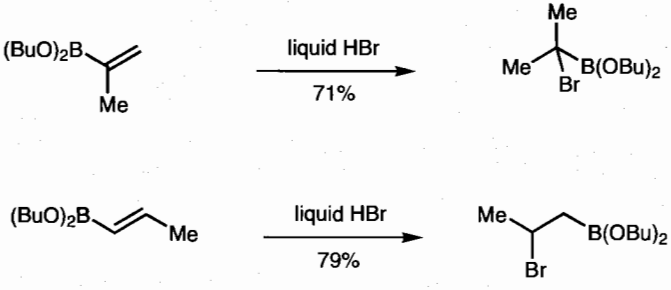


Scheme 9.2 Synthesis of 1-iodoalkenes from 1-alkenylboronic acids.

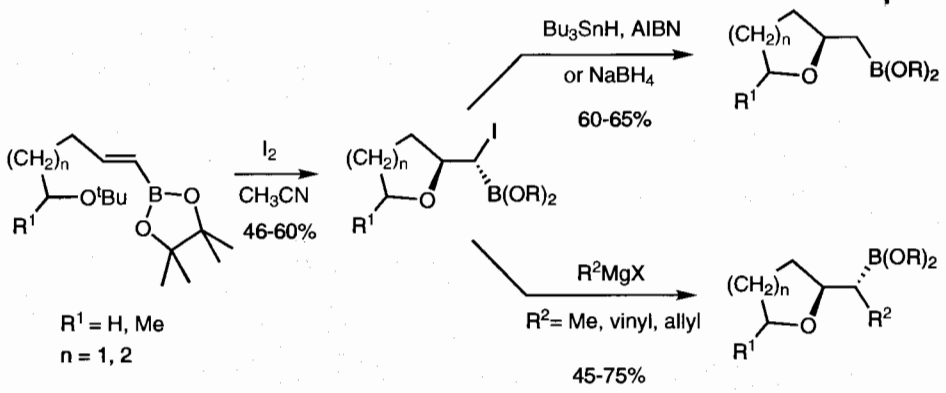
Halosuccinimides (NCS, NBS or NIS) have been used efficiently as substituents of halogens to synthesize the corresponding halides with conservation of geometry [7], while fluorine-containing alkenes were obtained by reaction with an electrophilic fluorinating agent, but as a mixture of geometrical isomers [8]. Other boron–heteroatom exchange reactions were also reported to afford, stereospecifically, vinylmercuric halides [9], vinyl(phenyl)iodonium tetrafluoroborates [10], vinylbismuthonium and telluronium salts [11], vinyl selenides [12] and vinyllead triacetates [13].

Electrophilic addition of hydrogen bromide to dibutyl prop-1-ene-2-boronate places the halogen predominately on the α-carbon [14]. The directing effect of the boronic ester group is weaker than that of a methyl group, as shown by the formation of the opposite regioisomer from dibutyl (*E*)-prop-1-ene-1-boronate (Scheme 9.3).

While intermolecular haloetherification of alkenylboronic esters is of limited synthetic interest, due to the lack of regioselectivity and the concomitant loss of boron, the intramolecular version has opened a new route to tetrahydrofuran- and tetrahydropyran-substituted α-iodoboronic esters (Scheme 9.4) [15].



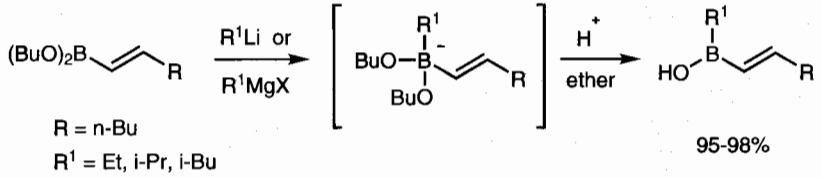
Scheme 9.3 Addition of hydrogen bromide to alkenylboronic esters.



Scheme 9.4 Intramolecular iodoetherification of alkenylboronic esters.

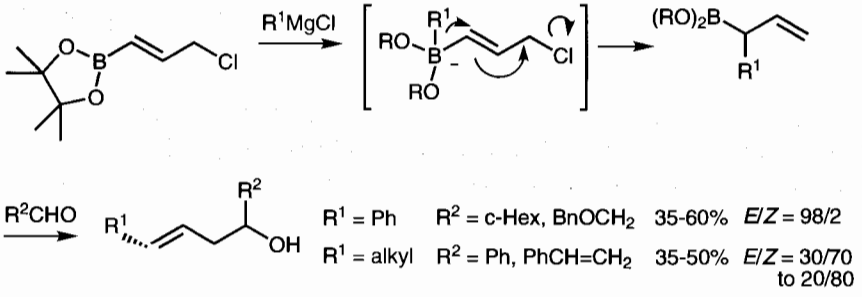
9.1.2
Addition of Organometallics

1-Alkenylboronic esters do not undergo conjugated addition like their analogous carboxylic esters, except when an electron-withdrawing group activates the double bond (see below). Instead, their reactions with organolithium and Grignard reagents provide efficient, selective access to the corresponding alkenylborinic derivatives via formation of "ate" complexes (Scheme 9.5) [16].



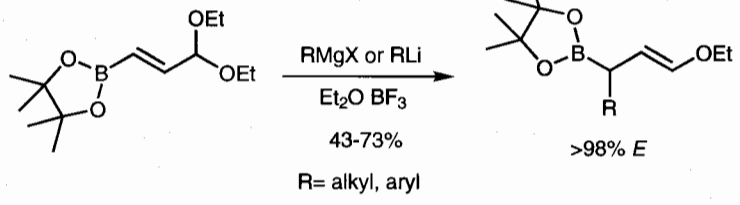
Scheme 9.5 Synthesis of alkenylborinic acids from alkenylboronates.

Similarly, (3-chloroprop-1-enyl)boronate treated with Grignard reagents affords the corresponding "ate" species. The presence of a leaving group in a γ-position induced a spontaneous rearrangement with migration of R^1 from boron to the α-alkenyl carbon atom (Scheme 9.6). A suitable choice of the diol component and reaction temperature allowed selective production of α- or γ-substituted allylboronates, which can be further trapped by aldehydes. A low degree of asymmetric induction has been observed with a (+)-pinanediol derivative [17]. A single geometric isomer was obtained when the substituent α to the halogen differed from hydrogen and it is also notable that the substitution occurred selectively in the γ-position with other nucleophiles such as amines, triphenylphosphine, lithium thiophenate and the lithium salt of a bislactim ether [18].



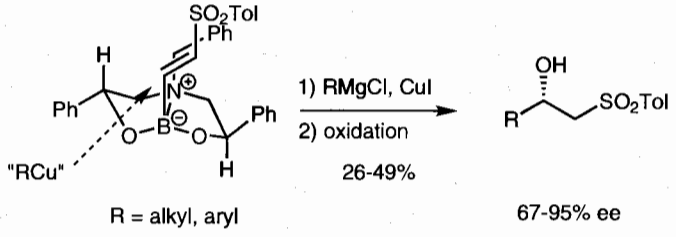
Scheme 9.6 Synthesis of homoallylic alcohols from (3-chloroprop-1-en-1-yl)boronate.

A similar approach was developed in a stereodefined synthesis of (*E*)-γ-alkoxyallyl α-substituted boronates from alkenyl boronates containing an acetal group [19]. Quaternarization of the boron atom at low temperature in the presence of a Lewis acid was followed, upon warming, by 1,2-migration of the alkyl or aryl group from the boron atom to the α-alkenyl carbon with concomitant displacement of an alkoxy group (Scheme 9.7).



Scheme 9.7 Stereoselective synthesis of γ-alkoxyallylboronates.

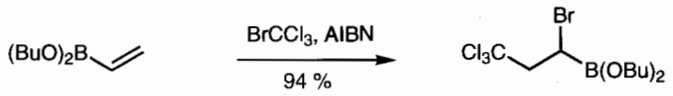
Boron has been protected from nucleophilic attack by intramolecular coordination in asymmetric Michael additions of organocuprates to acryloyl and vinylsulfonyl dioxazaborocines [20]. With an optically pure aminodiol, the enantiomeric purity was determined after oxidation of the carbon–boron bond. The greatest degree of asymmetric induction observed with a sulfone derivative was rationalized by an exo-approach of the organometallic reagent (Scheme 9.8).



Scheme 9.8 Michael addition of organocuprates to activated alkenyldioxazaborocines.

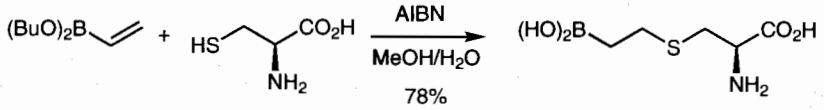
9.2
Radical Additions

The first discovered reactions at the double bond of alkenylboronates were additions of free radicals [21]. Bromotrichloromethane gave, after initiation with light or in the presence of azobisisobutyronitrile (AIBN), the corresponding α-bromoboronate in excellent yield (Scheme 9.9). These products were the first compounds of this class of boronic esters and the starting point of a rich chemistry [22]. Hydrogen bromide, under irradiation with ultraviolet light, led to 2-bromoethaneboronate [23, 24].



Scheme 9.9 Bromotrichloromethane addition to dibutyl vinylboronate.

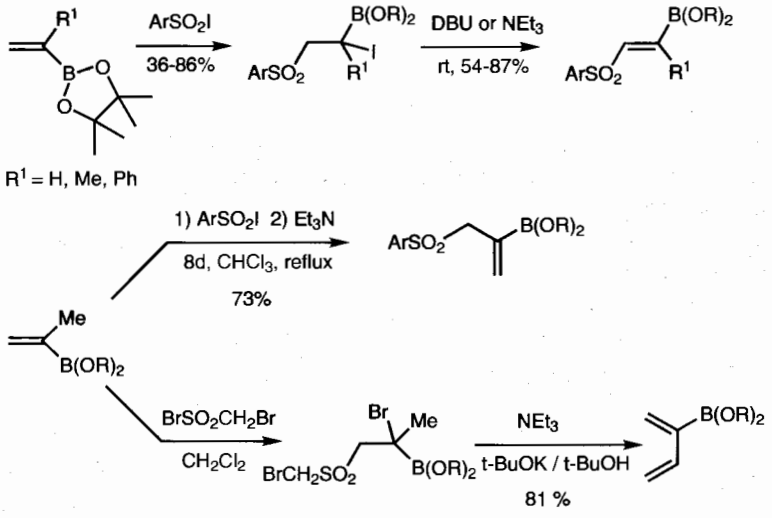
Hydrostannation reactions provided adducts with the organotin moiety at the β-carbon [25], while mercaptans readily yielded various β-alkylthioboronic esters [21]. This reaction has been exploited for the synthesis of several water-soluble boronic acids as potential agents in a Boron Neutron Capture Therapy strategy [26]. More recently, this approach was used to prepare new efficient arginase inhibitors (Scheme 9.10) [27].



Scheme 9.10 Radical addition of L-cysteine to dibutyl vinylboronate.

Sulfonyl iodides react with alkenyl- and 1,3-dienyl boronic esters to give adducts that afforded, upon treatment with base, new sulfonyl α,β-unsaturated boronates. The propenyl derivative deserves special comments since the corresponding allylsulfone has been obtained under heating at reflux in chloroform. By using bromomethanesulfonyl bromide, the parent buta-1,3-dienyl-2-boronic ester was synthesized via a vinylogous Ramberg–Backlung rearrangement of the corresponding β-bromosulfone (Scheme 9.11) [28].

Alkenyl boronic esters can also be used to trap nucleophilic carbon-centered radicals, which can be generated by the tin hydride method or by decomposition of an organomercurial derivative. The influence of the olefin and boron substituents on the reactivity and regioselectivity has been determined. Vinyl-9-BBN displayed significantly better reactivity than the boronic ester while the directing effect of the boronic ester group is weaker than that of an ester function. The Barton radical chain procedure furnished very stable adducts due to an intramolecular complexation between boron and nitrogen (Scheme 9.12) [29]. Radical additions of various xanthates also occurred smoothly in the presence of lauroyl peroxide [30]. Intermolecular ver-

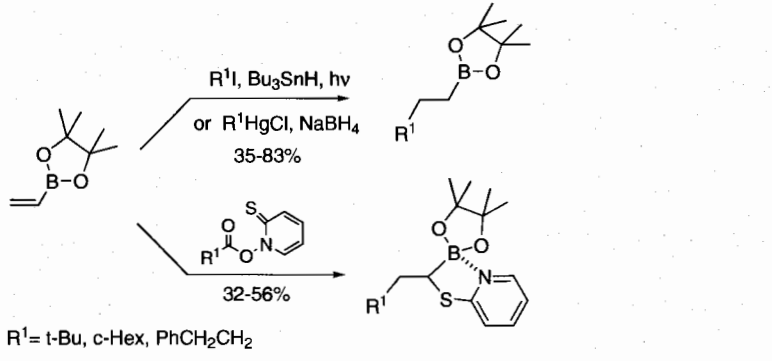


Scheme 9.11 Sulfonyl halide additions to alkenylboronates and transformations of the resulting adducts.

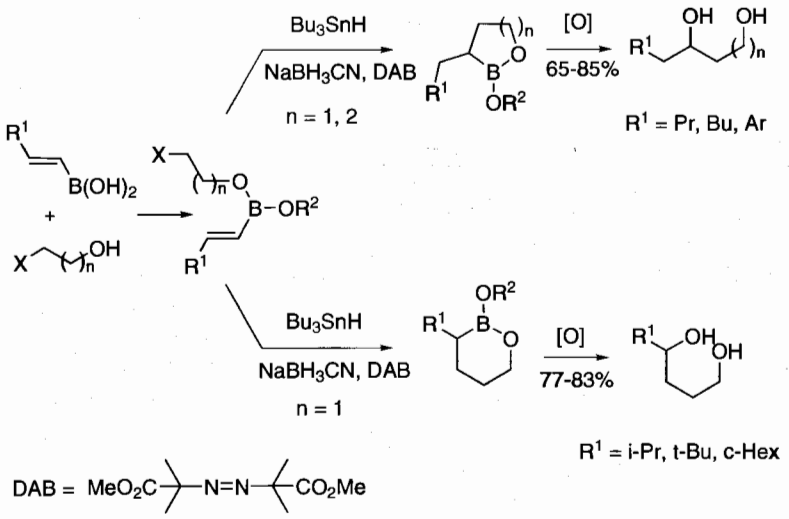
sions of these additions have been described as well as some transformations of the resulting carbocycles [29].

In a related process, boron-tethered radical cyclizations are a useful alternative to the widely used silicon versions. In some cases, rearranged products were produced as a result of an intramolecular S_Hi reaction of a carbon-centered radical at boron (Scheme 9.13) [31].

Addition of $Et_3Si^\bullet$ or $Me_3Sn^\bullet$ to a vinyl boronate generated radical-containing α-boronate substituents. These species have been observed by electron paramagnetic resonance spectroscopy, and the structures and energetics of α-boronate radicals were computed by density functional theory (DFT) methods (B3LYP/6-31G*) [32]. The computed bond dissociation energy [$(MeO)_2BCH_2$–H] was in excellent agreement with the analogous value derived from the experimental rotation barrier.

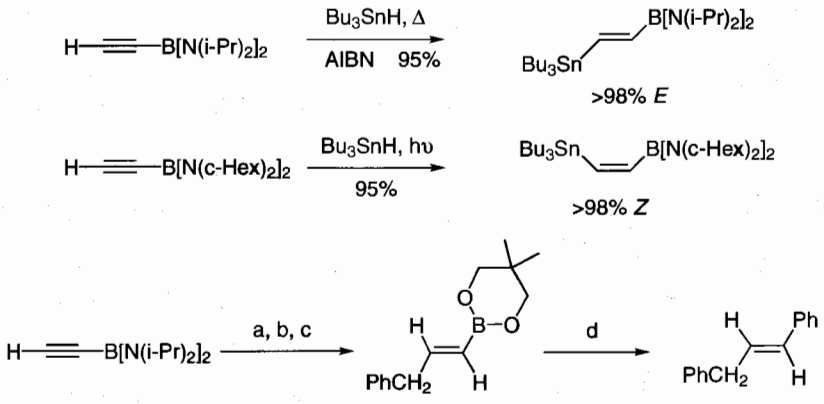


Scheme 9.12 Intermolecular addition of carbon-centered radicals to pinacol vinylboronate.



Scheme 9.13 Boron-tethered radical cyclizations.

Functionalized alkenyl diamino- and dialkoxyboranes have been produced regio- and stereoselectively through addition of carbon- or heteroatom-centered radicals (generated from bromotrichloromethane, thiols, phosphines and tributyltin hydride) to ethynylbis(diisopropylamino)boranes. The synthetic utility of these reactions was illustrated by the preparation of stereodefined (*Z*)- or (*E*)-alkenylboronic esters via palladium-catalyzed cross-coupling of the stannylated derivatives. The boronate moiety was retained in the Stille reaction and a Suzuki coupling under basic conditions can be further conducted (Scheme 9.14) [33].



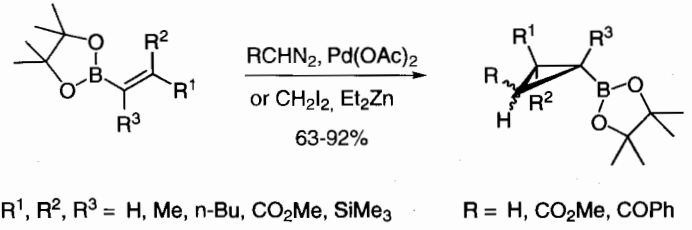
(a) Bu_3SnH, AIBN, 90°C, toluene. (b) $Pd(PPh_3)_4$, $PhCH_2Br$, toluene. (c) 2,2-dimethylpropan-1,3-diol, ether. (d) $Pd(PPh_3)_4$, PhI, toluene, 3N NaOH, overall yield 45%

Scheme 9.14 Radical additions to ethynylbis(diisopropylamino) borane.

9.3
Cycloaddition Reactions

9.3.1
Cyclopropanation

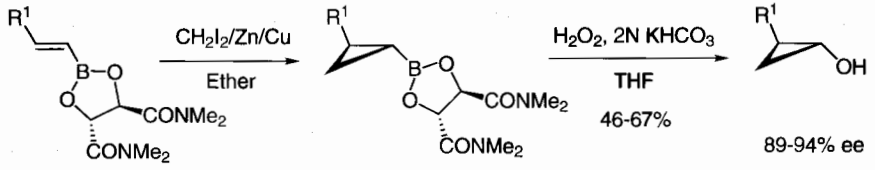
Cyclopropanes and their derivatives are versatile building blocks in organic synthesis. They are also present in many natural products and frequently included as substituents in the structure of new biologically active substances. While cyclopropylboranes have long been described [34], it is only since an efficient access to the boronic esters was reported that they really attracted chemist's interest. In 1989, the first additions of carbenes, generated from diazo compounds and palladium acetate, to pinacol alkenylboronic esters were reported to give racemic mixtures of cyclopropylboronates (Scheme 9.15) [35].



R^1, R^2, R^3 = H, Me, n-Bu, CO_2Me, $SiMe_3$ R = H, CO_2Me, COPh

Scheme 9.15 Carbene additions to alkenylboronic esters.

One year later, the first asymmetric cyclopropanation was realized by diastereofacial selective Simmons–Smith reaction to esters of tetramethyltartramide as diol instead of pinacol. Subsequent oxidation gave optically active 2-substituted cyclopropanols in 89–94% ee (Scheme 9.16) [36].

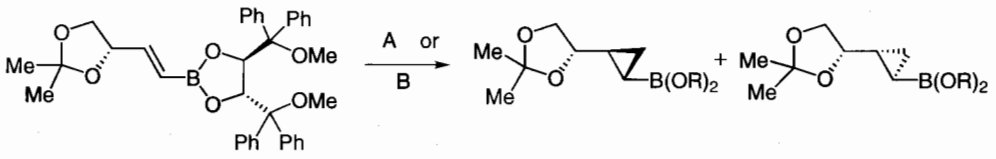


R^1 = n-Bu, Bn, Ph

Scheme 9.16 Asymmetric synthesis of cyclopropylboronates using a chiral director on the boron atom.

This auxiliary-controlled synthesis was later studied by others [37, 38] and (2*R*,3*R*)-1,4-dimethoxy-1,1,4,4-tetraphenyl-2,3-butanediol was proven to be both an efficient chiral director and protecting group in the cyclopropanation of boronic esters [39–42]. These compounds are stable on silica gel, which allows the chromatographic separation of the diastereoisomers. The influence of an additional stereogenic center in the side chain of the alkene has also been examined [43], as well as substrate-

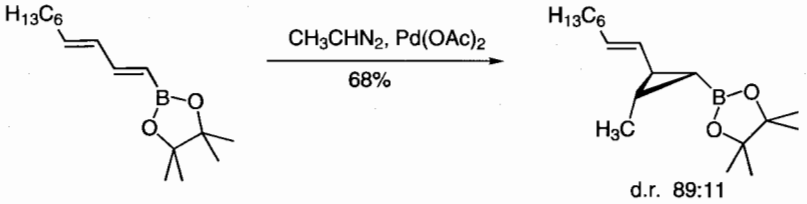
controlled diastereoselection of alkenyl boronic esters bearing an achiral diol (Scheme 9.17) [44].



Method A: CH_2N_2, $Pd(OAc)_2$	93%	83	/	17
Method B: CH_2I_2, $ZnEt_2$	58%	11	/	89

Scheme 9.17 Cyclopropanation of an alkenylboronic ester containing a chiral diol and an additional stereogenic center.

More recently, the reaction of dienylboronates with diazoalkanes in the presence of palladium acetate was described to afford regio-, chemo- and diastereoselectively the corresponding trisubstituted cyclopropanes (Scheme 9.18) [45].



Scheme 9.18 Cyclopropanation of dienylboronate using diazoalkanes in the presence of palladium acetate.

Further transformations of cyclopropylboronates by creation of a new carbon–carbon or carbon–oxygen bond have been largely developed, as well as the modification of the side-chain in the presence of the boronic ester functionality [46].

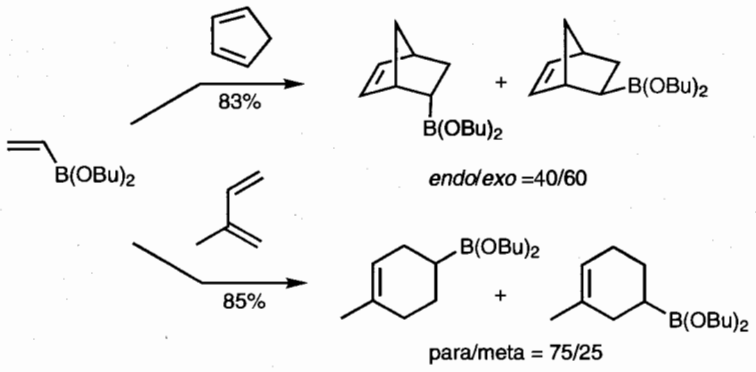
9.3.2 Diels–Alder Reactions

Due to their great versatility, boron-substituted dienophiles and dienes have emerged as attractive building blocks in Diels–Alder reactions [47]. In this section, we review the most important results related to the [4+2] cycloadditions involving alkenyl, alkynyl and dienyl boronic esters and some of their derivatives.

9.3.2.1 Alkenylboronates as Dienophiles

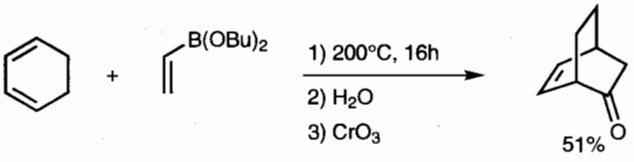
The use of vinylboronates as dienophiles was first reported for dibutyl ethyleneboronate and cyclopentadiene. At 90–100 °C, a mixture of dibutyl *endo*-and *exo*-5-

norbornene-2-boronates was obtained in good yield [48]. Isoprene reacted at a higher temperature (140 °C) to afford a 75:25 mixture of regioisomers (Scheme 9.19) [49].



Scheme 9.19 [4+2] cycloaddition of dibutyl(ethylene)boronate to cyclopentadiene and isoprene.

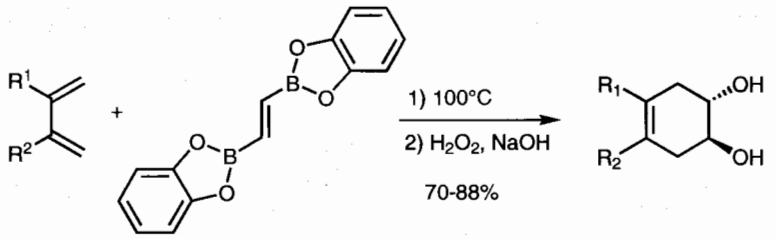
The carbon–boron bond of the cycloadducts can be efficiently oxidized and this dienophile can thus be considered as a formal hydroxyethylene equivalent. An example of this strategy is the synthesis of (±)-dihydrocannivanine derivatives from 1,3-cyclohexadiene. Without purification, the boronate ester was hydrolyzed and oxidized with Jones reagent to afford the corresponding ketone (Scheme 9.20) [21, 50].



Scheme 9.20 Diels–Alder approach for a total synthesis of (±)-dihydrocannivanine.

In the same way, *trans*-1,2-bis(catecholboronyl)ethylene, a reportedly air-stable, crystalline solid, is a useful (*E*)-dihydroxyethylene equivalent [51]. This alkene is more reactive than the monosubstituted derivative and reacts conveniently with simple acyclic dienes at 100 °C. Oxidation of the cycloadducts proceeded cleanly to give the corresponding diols in good yields (Scheme 9.21).

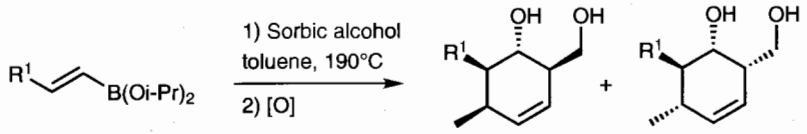
However, these alkenylboronic esters can be considered as poor dienophiles compared to the corresponding dialkylboranes since high temperatures were generally required to afford cycloadducts with low regio- and stereoselectivities. The great reactivity of vinyldialkylboranes in Diels–Alder reactions cannot be rationalized by means of FMO theory and the high endo stereoselectivity suggests the presence of an important [4+3] interaction in the transition state. This hypothesis has been confirmed by ab initio calculations [47a].



R^1, R^2 = H, Me, t-Bu, Ph, cyclopentadiene

Scheme 9.21 Synthesis of *trans*-cyclohexenediols from (*E*)-1,2-bis(catecholboryl)ethylene.

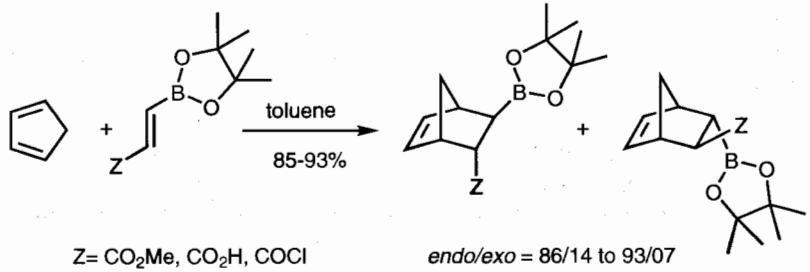
In the intramolecular approach, alkenyl boronic acids acted both as template and source of dienophile (Scheme 9.22) [52]. When sorbic alcohol was used as diene, oxidation without purification of the bicyclic intermediates afforded functionalized cyclohexenes with a good endo-selectivity. Other versions involving alkenylboranes were also reported [53].



R^1 = Ph, 90/10, 84%
R^1 = n-Bu, 70/30, 65%

Scheme 9.22 Boron-tethered intramolecular Diels–Alder reactions.

The adjunction of a β-electron-withdrawing group significantly increased the reactivity of alkenyl boronic esters [54]. The resulting electron-deficient dienophiles were more reactive towards simple 1,3-dienes than simple vinylboronic esters (Scheme 9.23). For instance, the sulfonyl derivative in the presence of cyclopentadiene reacted



Z= CO_2Me, CO_2H, COCl
p-$MeC_6H_5SO_2$, CHO

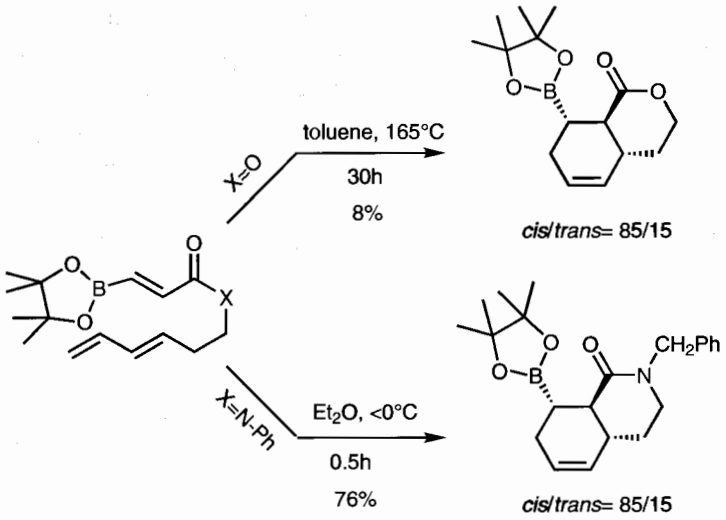
endo/exo = 86/14 to 93/07

Scheme 9.23 Diels–Alder reactions of activated alkenylboronates with cyclopentadiene.

at room temperature to afford two diastereoisomers, the major one exhibiting the electron-withdrawing group in the endo position. Cycloadditions with other 1,3-dienes also proceeded in good yields at higher temperature, typically 80 to 110 °C to give a 1:1 mixture of regioisomers in the case of isoprene.

Synthetically, 3-boronylpropenoic acid derivatives are very attractive dienophiles because they can be considered as (*E*)-β-hydroxyvinylamine equivalents if a Curtius reaction is carried out [55].

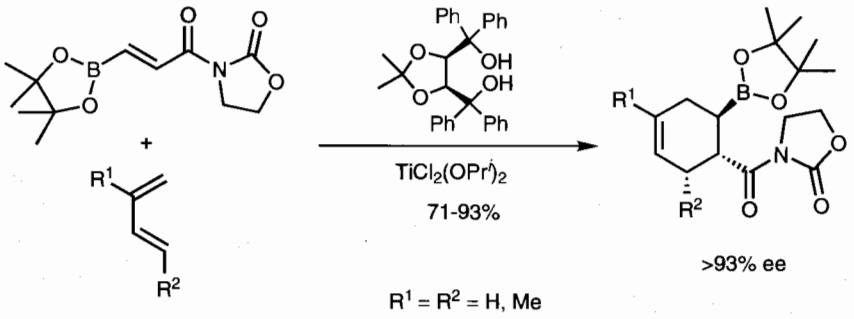
Intramolecular versions of these Diels–Alder reactions have been explored. With ester derivatives, harsh conditions were necessary to observe cyclization, leading to cycloadducts in low yields. Conversely, trienyl amides give adducts in high diastereoselectivity and good yields under mild conditions (Scheme 9.24). Notably, the introduction of a chiral unit on nitrogen or on boron led to poor diastereoselectivity [56].



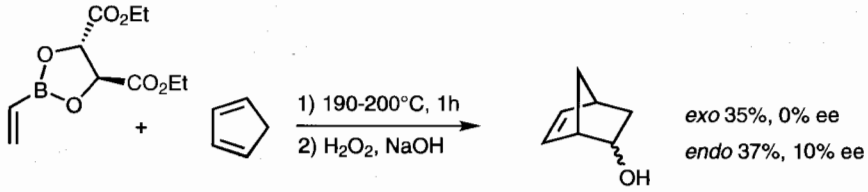
Scheme 9.24 Intramolecular Diels–Alder reactions involving 3-boronylpropenoic acid derivatives.

A few studies reporting an asymmetric Diels–Alder reaction involving vinylboronates have been hitherto published. A catalytic asymmetric cycloaddition has been developed using 3-(3-boronyl-propenoyl)-1,3-oxazolidin-2-ones as dienophiles and a chiral titanium catalyst in the presence of molecular sieves [57]. Adducts were obtained as single isomers in good yield and high enantioselectivity (>93% ee) (Scheme 9.25). Cyclopentadiene gave a mixture of endo and exo isomers (~95:5).

Asymmetric induction through the attachment of chiral ligands on the boron atom was examined with (+)-diethyltartrate derivatives (Scheme 9.26) [58]. All the alcohols obtained by oxidation (except the exo products) were optically active. The fact that only endo products show optical activity could be explained by a [4+3] transition state, as already postulated by others [59]. However, the observed optical purities were very low.

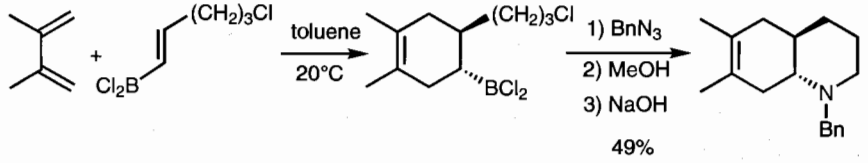


Scheme 9.25 Asymmetric Diels–Alder reaction catalyzed by a chiral titanium reagent.



Scheme 9.26 Asymmetric [4+2] cycloaddition using a chiral alkenylboronate.

Reactivity was enhanced remarkably with the more electrophilic alkenyldichloroboranes [60]. Moreover, amination with azides gave the corresponding amines in good yields. With a halogen atom in the appropriate position, ring closure of intermediate ω-halogenoalkylamines can be realized by treatment with base to afford bicyclic pyrrolidines and piperidines with a trans junction (Scheme 9.27) [61].

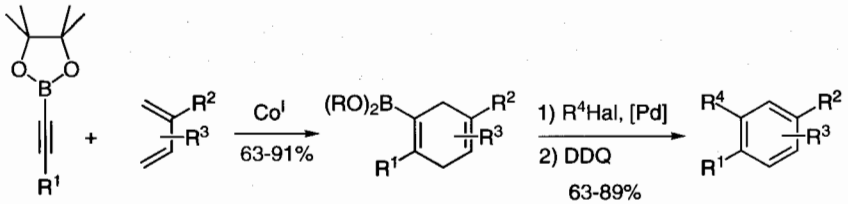


Scheme 9.27 Alkenyldichloroboranes as precursors of bicyclic piperidines.

9.3.2.2 **Alkynylboronates as Dienophiles**

Dibutyl acetyleneboronate is a moderately active dienophile since the Diels–Alder adduct with cyclopentadiene was obtained in a 25% yield after heating at 130 °C for 15 h [62]. In contrast, alkynyldibromoboranes, generated in situ by silicon/boron exchange, appeared to be highly reactive dienophiles [63]. Unfortunately, their great electrophilicity restricted their synthetic application to unfunctionalized substrates.

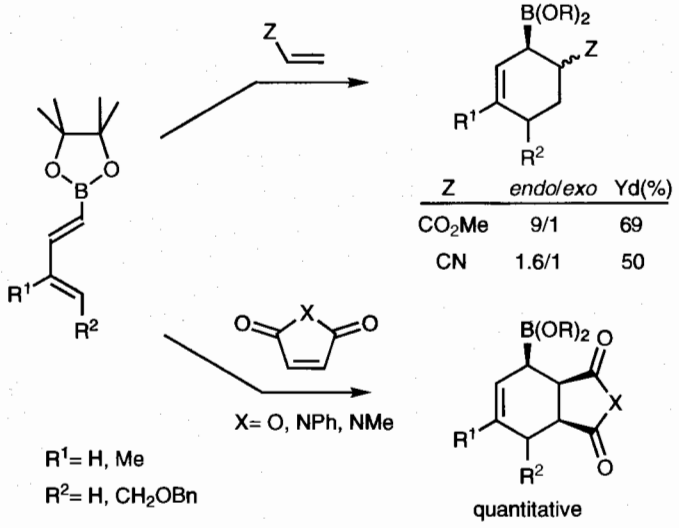
Cobalt-catalyzed Diels–Alder reactions offer an interesting alternative since the cycloadditions are carried out under mild conditions. With isoprene, alkynylboronic esters predominantly gave the regioisomer in which the methyl group of the diene and the boronic ester functionality are meta related [64]. Subsequent Suzuki coupling reactions can be performed without isolation of the intermediates (Scheme 9.28).



Scheme 9.28 Cobalt-catalyzed Diels–Alder reactions involving alkynylboronates.

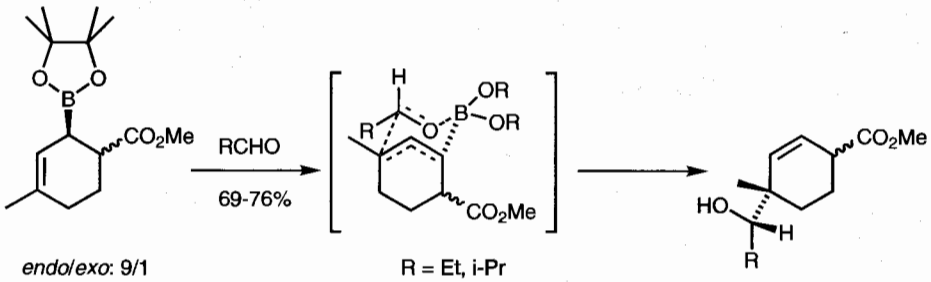
9.3.2.3 1,3-Dienyl-1-boronates as Dienes

Diels–Alder cycloaddition involving 1,3-dienylboronates was first reported in 1987 [65]. These dienes react with activated dienophiles such as maleic anhydride and maleimides at relatively high temperature (toluene, 80 °C) to give exclusively the endo cycloadducts (Scheme 9.29). A mixture of diastereoisomers was obtained regioselectively with methyl acrylate or acrylonitrile. The endo selectivity was significantly increased when the reaction was performed without solvent [66].



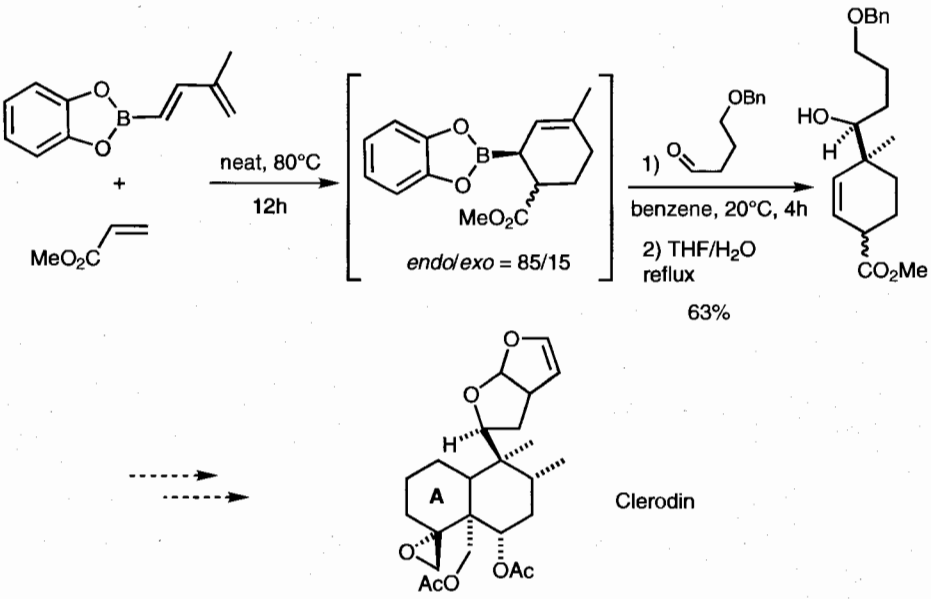
Scheme 9.29 Diels–Alder reactions of 1,3-dienylboronates.

These reactions offer numerous possibilities for further stereocontrolled transformations. For example, oxidation with amine-*N*-oxide afforded the corresponding β-hydroxyesters. Moreover, the synthetic potential of this Diels–Alder reaction is greatly amplified by the presence of an allylboronate fragment in the resulting adducts. The reaction with aldehydes occurred at room temperature with a high stereocontrol, in agreement with a Zimmerman–Traxler-type chair-like transition state (Scheme 9.30).



Scheme 9.30 Allylation reaction with the Diels–Alder cycloadduct of a 1,3-dienylboronate and methyl acrylate.

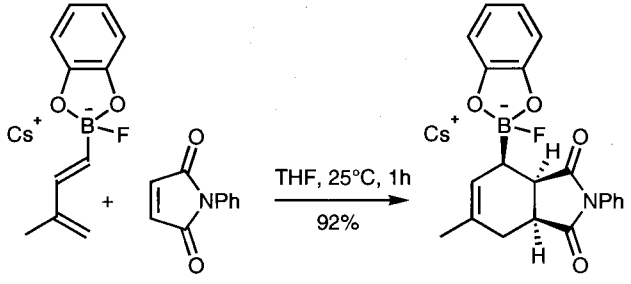
The one-pot cycloaddition/allylboration sequence has also been carried out to trap the apparently unstable intermediates and afford the corresponding alcohols directly after hydrolysis. The diastereoselectivity is similar to that observed using the previous two-step methodology [67]. This tandem reaction was used towards the synthesis of complex natural products such as clerodin (Scheme 9.31) [68].



Scheme 9.31 Synthesis of an advanced clerodin intermediate through a tandem Diels–Alder/allylboration sequence.

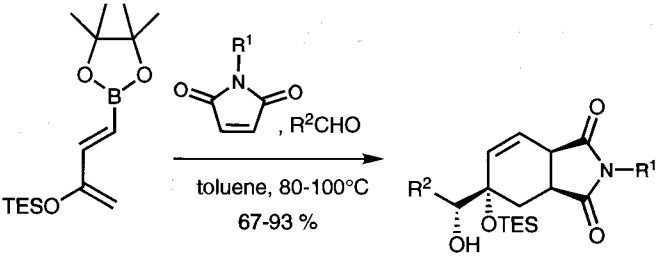
However, this Diels–Alder/allylboration sequence suffered some limitations due to the low reactivity of 1,3-dienylboronates, which required highly activated dienophiles. Semi-empirical and ab initio calculations have been realized to explain the reactivity of 1,3-dienylboronates towards methyl acrylate [69].

Different approaches were investigated to overcome this problem. The first strategy reported in 1991 was based on the use of a chiral aminodiol. Donation of electrons from nitrogen to boron activates the diene and accelerates the addition to activated olefins compared to its boronic ester analogue [70]. The endo cycloadducts were exclusively produced with *N*-phenyl maleimide at room temperature. A low asymmetric induction was observed with dienes derived from N-substituted amino acid (12% ee) [71]. Ate complexes prepared by quaternarization of a catechol derivative with a stoichiometric amount of CsF are highly reactive in these cycloaddition reactions (Scheme 9.32) [72].



Scheme 9.32 Diels–Alder reaction of a 1,3-dienylborate salt with *N*-phenylmaleimide.

The influence of an electron-donating ether substituent on the butadiene framework was studied a few years later [73]. Different isomers have been synthesized and tested in a model one-pot [4+2]/allylboration. Unlike 1-borono-4-methoxybutadiene pinacolate, which failed to provide the allylation product, the 3-triethylsiloxy derivative in presence of maleimides and aldehydes gave the corresponding hydroxyalkylated cyclohexenes (Scheme 9.33). A single diastereoisomer was isolated in all cases.



R^1= Ph, Me

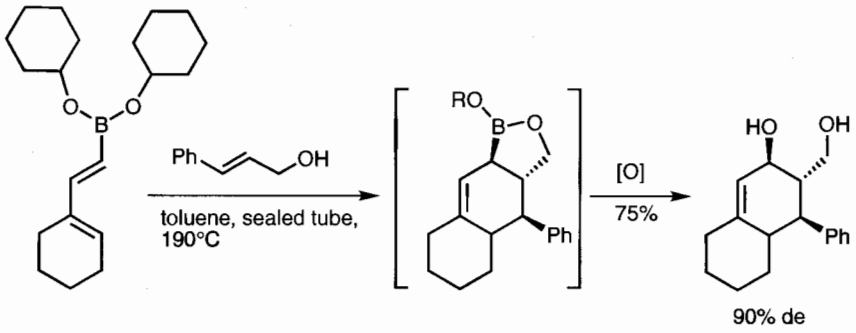
R^2= C_6H_5, *p*-NO_2-C_6H_4, *p*-MeO-C_6H_4, i-$PrCH_2$, *p*-Br-C_6H_4

Scheme 9.33 Synthesis of hydroxylated cyclohexenes via tandem [4+2] cycloaddition/allylboration.

However, the reactivity of these electronically enriched dienes seems to be still insufficient to observe reactions with moderately activated dienophiles under mild conditions.

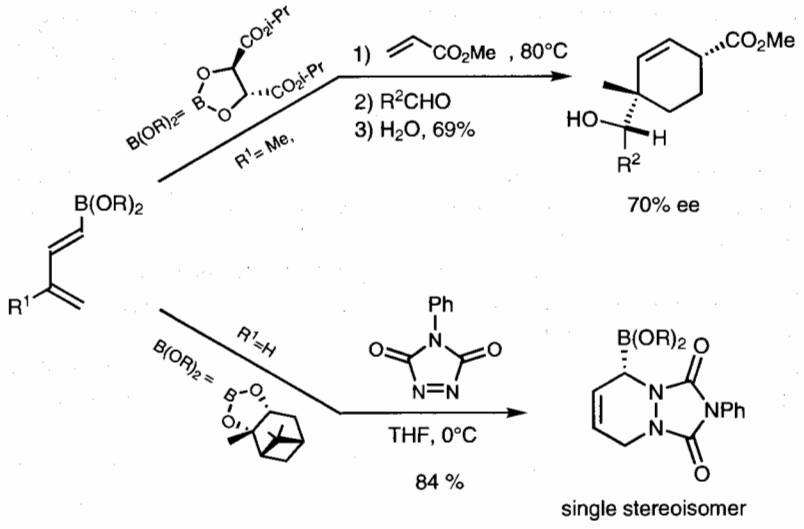
Another strategy used to overcome the low activating effect of the boronate substituent was to add Lewis acids to activate the dienophile [74]. With methyl acrylate and a stoichiometric amount of $EtAlCl_2$, the reaction occurred at a lower temperature (20 °C, CH_2Cl_2) and shorter reaction time (6 h) to afford the cycloadduct in a better stereocontrol (endo/exo >95:5).

As expected, the reactivity of 1,3-dienylboronates was increased considerably in intramolecular versions. Tethering of dienylboronate precursors to an unactivated dienophilic component allowed in situ formation of mixed boronic esters, followed by intramolecular Diels–Alder reaction and oxidation to the corresponding cyclohexene diols (Scheme 9.34). The reactions were highly regioselective and the diastereoselectivity varied with the nature of the substituents on the dienophile [75].



Scheme 9.34 Boron-tethered intramolecular Diels–Alder reaction of 1,3-dienylboronates.

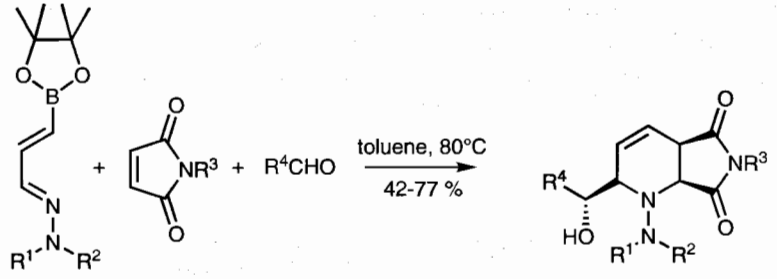
Different studies were carried out to develop diastereocontrolled versions of these Diels–Alder reactions. Better results were obtained when an optically pure diol was used as chiral director. The tandem reaction involving a 1,3-dienylboronate derived from tartrate esters proceeded with 70% enantiomeric excess (Scheme 9.35) [76]. The hetero-Diels–Alder reaction of enantiomerically pure (+)-pinanediol 1,3-dienylboronate with an azo dienophile gave the *R*-configured endo cycloadduct as the single stereoisomer [77].



Scheme 9.35 Asymmetric Diels–Alder reaction of chiral 1,3-dienylboronates.

9.3.2.4 1,3-Dienyl-1-boronates as Heterodienes

A simple, efficient multicomponent sequence was recently developed to synthesize α-hydroxyalkylpiperidine derivatives from a 4-boronohydrazonodiene, maleimides and aldehydes (Scheme 9.36) [78]. The high diastereoselectivity of these tandem reactions can be explained by a complete endo-selectivity in the first step and a cyclic chair-like transition state in the allylboration reaction. The absolute stereochemistry of the final products can be controlled by using an optically pure 1-aza-4-borono-1,3-butadiene. This multi-component reaction can also be realized on a solid support, using an *N*-arylmaleidobenzoic acid functionalized resin. Very recently, this process

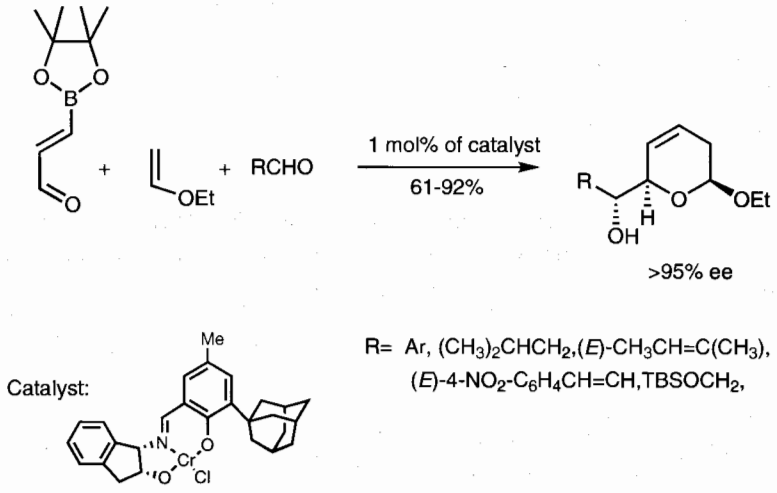


R^1= Me, H R^2= Me, Ph, Ac R^3= Me, Ph R^4= Ar,i-PrCH$_2$

Scheme 9.36 A tandem aza [4+2] cycloaddition/allylboration for the synthesis of α-hydroxylated piperidine derivatives.

was adapted to access 2,6-disubstituted piperidine units using Waldner's chiral sulfinimide dienophiles [79].

Cycloaddition reactions involving (*E*)-3-boronylacrolein as diene also opened a wide field of synthetic applications. In the racemic series, this heterodiene reacted with ethyl vinyl ether in the presence of a Lewis Acid, $Yb(fod)_3$, according to an inverse electron demand hetero-Diels–Alder reaction [80]. Aldehydes were added to the resulting allylboronates to give the homoallylic alcohols with a high diastereoselectivity. The asymmetric version of this tandem hetero [4+2] cycloaddition/allylboration was then improved spectacularly (Scheme 9.37). A catalyst made of a tridentate (Schiff base) chromium(III) complex allowed access to a series of 2,6-disubstituted dihydropyrans with high diastereo-and enantiomeric purity [81, 82]. As in the racemic series, a one-pot transformation was possible provided less catalyst (1 mol%) was used [81]. Notably, this is the only known report of a catalytic enantioselective [4+2] cycloaddition/allylboration process. This powerful process has been used in the synthesis of natural products such as a mosquito pheromone [81] and goniodiol [19b].

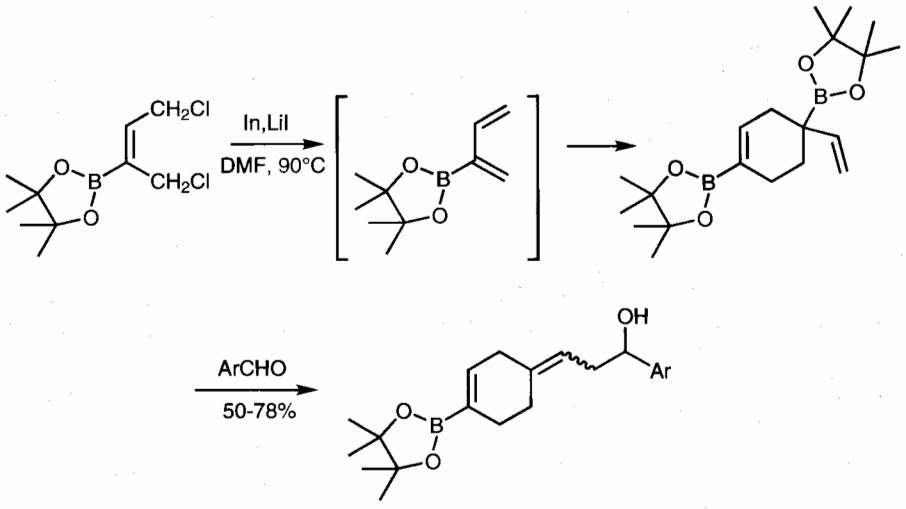


Scheme 9.37 Asymmetric synthesis of α-hydroxylated dihydropyrans via a catalytic hetero-Diels–Alder cycloaddition/allylboration sequence.

9.3.2.5 1,3-Dienyl-2-boronates as Dienes

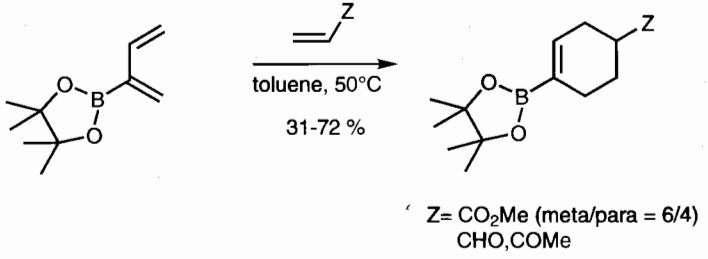
Few works reported the reactivity of simple 1,3-dienyl-2-boronates in Diels–Alder reactions. Unlike their 1-substituted analogues, they showed a high propensity to dimerize even at room temperature, like their ester or sulfone congeners (Scheme 9.38) [83]. A theoretical study of this dimerization showed that this process occurred in a highly regioselective way, giving a new allylboronate that further reacted in a one-pot sequence with aldehydes [84].

However, the parent unsubstituted diene can be isolated in high purity by a quick trap-to-trap distillation in high vacuo [83]. It is more reactive than the corresponding 1,3-dienyl-1-boronate and the addition to moderately activated dienophiles (acrolein,



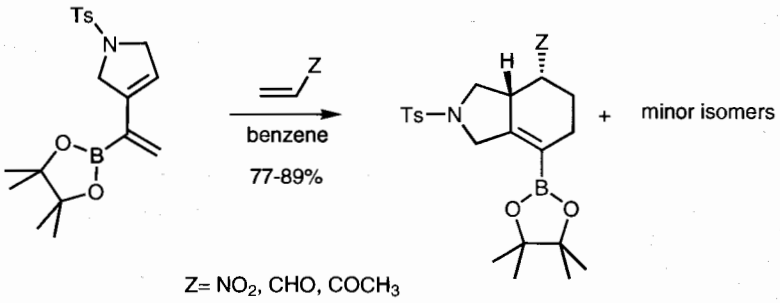
Scheme 9.38 Diels–Alder dimerization/allylboration sequence for the construction of cyclic alkenylboronates .

methyl vinyl ketone) generally proceeded at 50 °C to afford the 1,4-disubstituted products regioselectively, except with methyl acrylate (Scheme 9.39). A higher temperature was required with a more stable polysubstituted diene [85]. The only attempt to develop an asymmetric version of this Diels–Alder reaction using (+)-pinanediol as chiral director gave a mixture of two diastereoisomers in a nearly 1:1 ratio [83a].



Scheme 9.39 Cycloaddition reaction of pinacol (1,3-butadien-2-yl)boronate to dienophiles.

Cyclic 1,3-dienyl-2-boronates, prepared via a ring-closing metathesis reaction, have been described [86]. Treatment with an excess of dienophile (nitroethylene, acrolein, methyl vinyl ketone) furnished in all cases one major product; the minor components being the β-epimer and the endo regioisomer (Scheme 9.40).



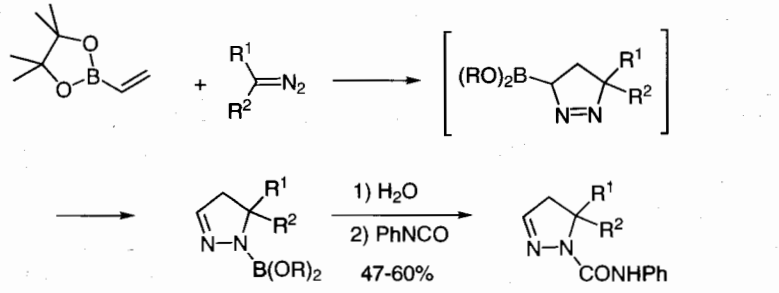
Scheme 9.40 Diels–Alder cycloaddition of a cyclic 1,3-dienyl-2-boronate.

9.3.3
1,3-Dipolar Cycloadditions

Alkenyl boronic esters have been shown to be good dipolarophiles in a range of 1,3-dipolar cycloadditions, thus giving access to boron functionalized heterocycles, which can be further engaged in various transformations.

9.3.3.1 Diazoalkanes

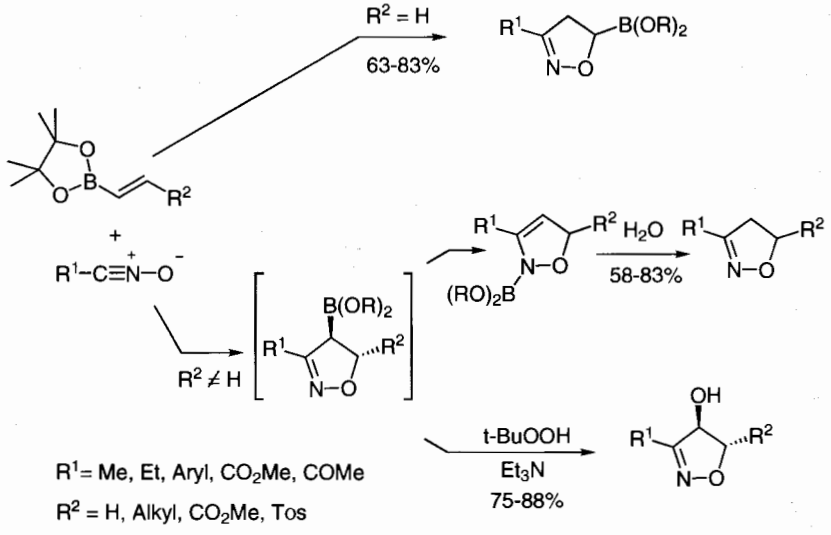
The addition of ethyl diazoacetate and diphenyldiazomethane to dibutyl vinylboronate was first reported over forty years ago [87]. This initial study was completed later to establish the scope and limitations of these reactions and the exact nature of the intermediates involved [88]. The regioselective cycloaddition step was immediately followed by a spontaneous 1,3-migration of boron to give a *N*-boronyl 2-pyrazoline, which can be trapped, after hydrolysis, with phenylisocyanate (Scheme 9.41).



Scheme 9.41 1,3-Dipolar cycloaddition of diazoalkanes to pinacol vinyl boronate.

9.3.3.2 Nitrile Oxides

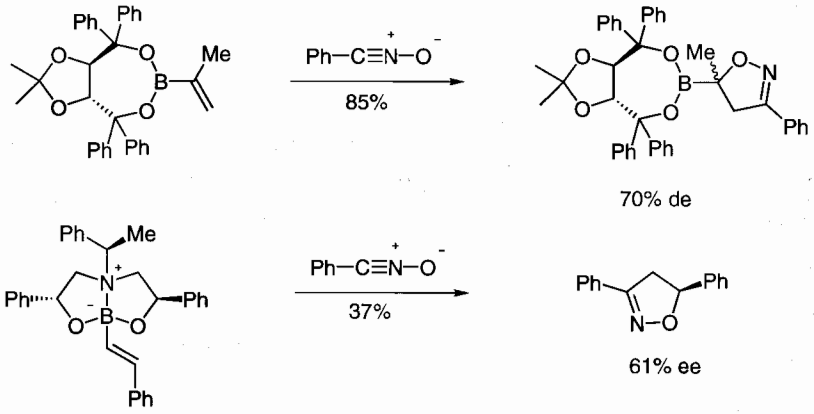
3-Aryl-5-isoxazoline boronic acids were first synthesized via 1,3-dipolar cycloadditions of pure nitrile oxides to dibutyl vinylboronate in 1966 [89]. More recently, the possibility of carrying out these reactions with dipoles generated in situ from nitroalkanes was explored successfully [90]. With 1,2-disubstituted alkenylboronic esters, the regioselectivity was reversed and, as previously observed with diazoalkanes, a spontaneous 1,3-boratropy occurred that caused the loss of boron after hydrolysis. However, careful oxidation of the reaction mixture before work-up afforded the corresponding 4-hydroxy-2-isoxazolines in good yields (Scheme 9.42) [91].



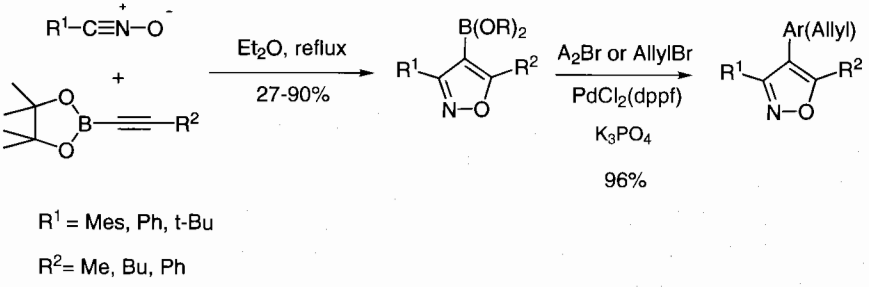
Scheme 9.42 Nitrile oxide cycloadditions to alkenylboronic esters.

Optically active cycloadducts have been prepared in a one-pot strategy, by using a camphorsultam substituted vinylboronic ester and sodium percarbonate used for nitrile oxide generation, oxidation of the intermediate and cleavage of the chiral auxiliary [92]. Chiral vinylboronic ester, derived from (+)-mannitol, gave only moderate diastereoselectivity [93]. Several chiral diols were also introduced on the boronic group to give, with 2-propenyl- and α-styrylboronate respectively, a 8:1 and 5:1 mixture of diastereoisomers [94]. In a related approach, vinyldioxazaborocines derived from a C_2 symmetric ligand have been synthesized and assayed, giving a 61% enantiomeric excess in the best cases (Scheme 9.43) [95].

Similarly, the cycloaddition reaction of nitrile oxides to alkynylboronates has been exploited to provide isoxazoleboronic esters with good levels of regiocontrol. These synthetic intermediates participate efficiently in Suzuki cross-coupling reactions (Scheme 9.44) [96, 97].



Scheme 9.43 Asymmetric cycloadditions of a nitrile oxide using a chiral director on a boron atom.



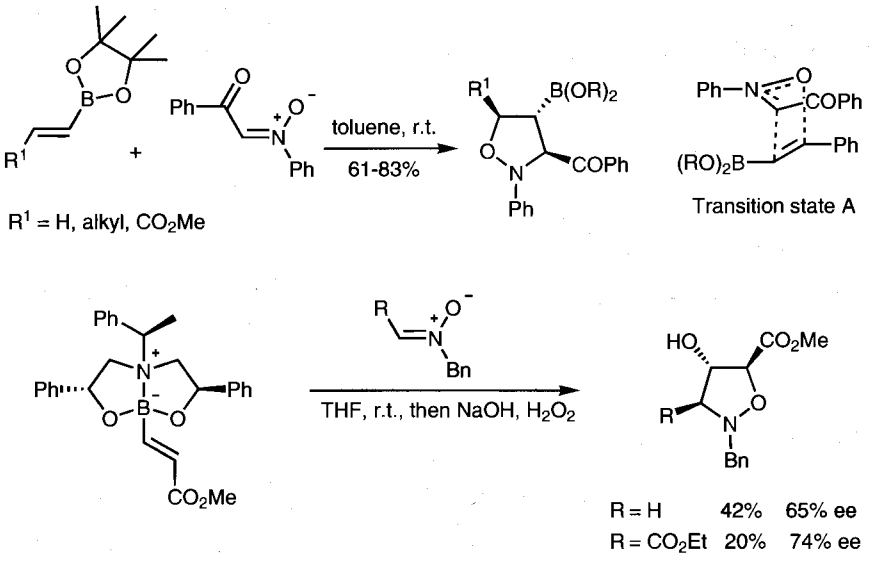
R^1 = Mes, Ph, t-Bu

R^2= Me, Bu, Ph

Scheme 9.44 A cycloaddition route to isoxazole boronic esters.

9.3.3.3 Nitrones

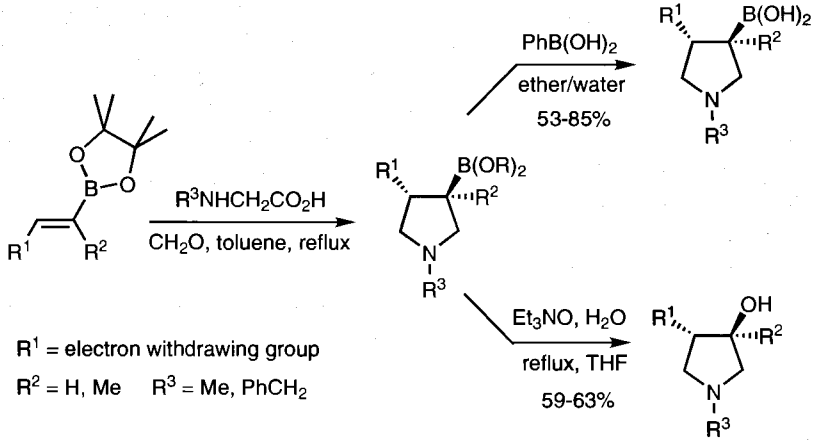
Alkenylboronic esters undergo regio- and stereoselective 1,3-dipolar cycloadditions with nitrones to provide boronic ester substituted isoxazolidines. These heterocycles present a trans relationship between substituents at the C_3–C_4 stereocenters and between H_4 and H_5, which suggests a preferred transition state A. Oxidation of the B–C bond with hydrogen peroxide yielded the corresponding 4-hydroxy derivatives (Scheme 9.45) [98]. For reactions conducted with chiral dioxazaborocines, the enantiomeric purities of the hydroxyisoxazolidines were around 70% ee (Scheme 9.45) [95].



Scheme 9.45 Nitrone cycloadditions to alkenylboronic esters and a chiral vinyl dioxazaborocine.

9.3.3.4 Azomethyne Ylides

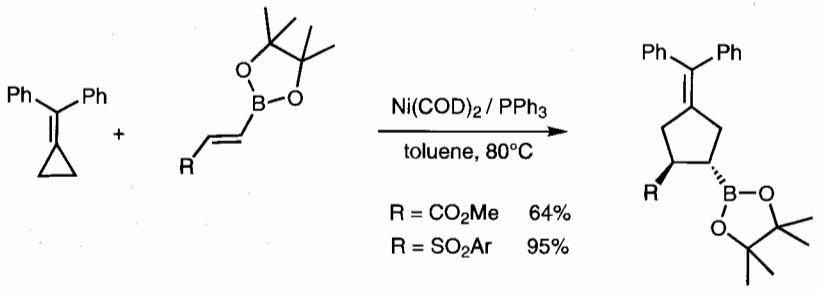
Substituted boron analogues of β-proline were synthesized efficiently via 1,3-dipolar cycloadditions of azomethyne ylides, generated from *N*-alkyl amino acids and formaldehyde, to alkenyl boronates. Heterocyclic cycloadducts were also good precursors of the corresponding pyrrolidin-3-ols by oxidation with triethylamine oxide (Scheme 9.46) [99].



Scheme 9.46 1,3-Dipolar cycloadditions of azomethyne ylides to alkenylboronates.

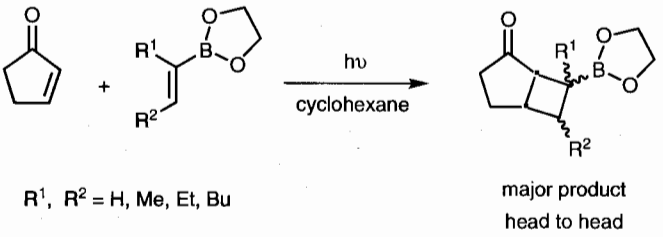
9.3.4
Other Cycloadditions

Alkenylboronates activated with either an ester or a sulfone group have been engaged in [3+2] cycloadditions with methylenecyclopropanes to afford methylenecyclopentanes in good yields. The cycloaddition reactions were highly stereoselective and yielded exclusively the corresponding trans-disubstituted products. The carbon–boron bond of the cycloadducts can be further transformed by oxidation to give the corresponding cyclopentanols (Scheme 9.47) [100].



Scheme 9.47 Nickel(0)-catalyzed [3+2] cycloadditions to vinylboronates.

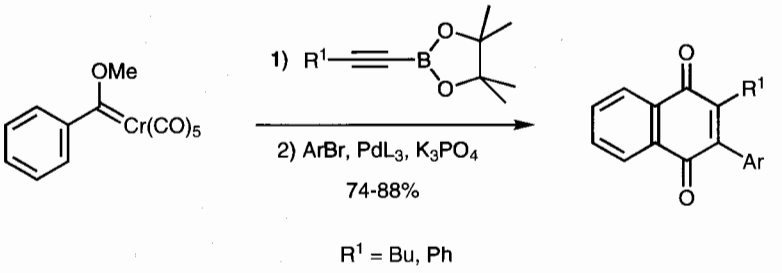
Participation of alkenyl boronates in intermolecular [2+2] enone-olefin photocycloadditions has been demonstrated with cycloalkenones. The major photoadducts with cyclopentenone resulted from head-to-head addition (Scheme 9.48) [101].



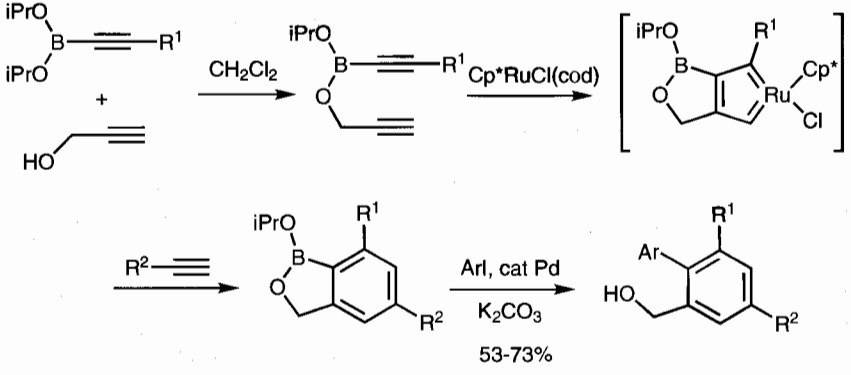
Scheme 9.48 Use of alkenylboronates in [2+2] enone-olefin photocycloadditions.

A novel class of quinone boronic esters has been prepared via a Dötz annulation of Fischer carbene complexes with alkynylboronates. The origin of the high regioselectivity is discussed in terms of steric and electronic effects. Additionally, these compounds undergo Pd-catalyzed coupling reactions to give substituted quinones and hydroquinones (Scheme 9.49) [102].

Chemo- and regioselective ruthenium-catalyzed cyclotrimerization of alkynes was accomplished through a temporary boron tether. Crude aryl boronates were obtained in a one-pot procedure in which they were subjected to a Suzuki–Miyaura coupling with aryl halides (Scheme 9.50) [103].



Scheme 9.49 Synthesis of quinone boronic esters via a regioselective Cr-mediated benzannulation and their application in Pd-catalyzed coupling processes.

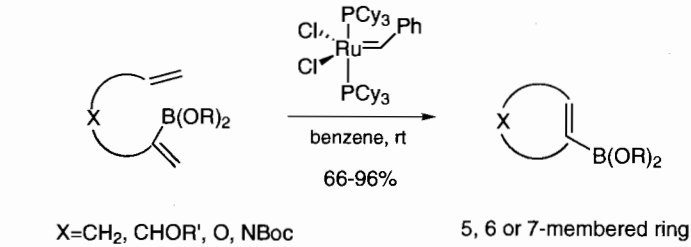


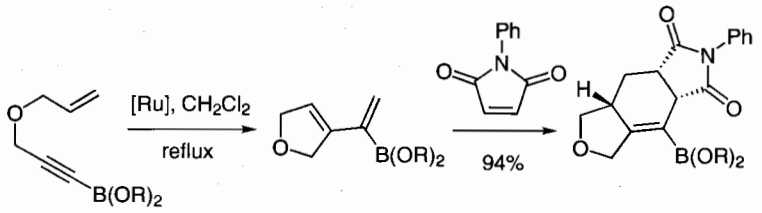
Scheme 9.50 One-pot four-component reactions via cyclotrimerization/Suzuki–Miyaura coupling.

9.4 Metathesis Reactions

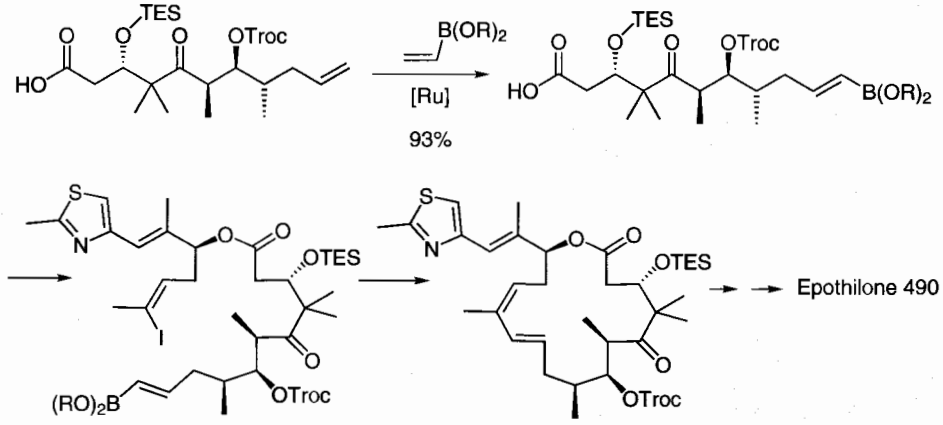
Since the 1990s, the olefin metathesis reaction has become a major synthetic tool in organic chemistry. Organoboranes were first employed in the construction of carbocyclic and heterocyclic alkenylboronates by ring closure of the corresponding acyclic precursors [104]. Ruthenium-catalyzed enyne metathesis of acetylenic boronates was later demonstrated as a concise route for the construction of cyclic 1,3-dienylboronic esters, which can be further engaged in [4+2] cycloadditions (Scheme 9.51) [86].

In the intermolecular process, cross-metathesis offers a useful and versatile alternative to alkyne hydroboration for the synthesis of functionalized alkenyl pinacol boronates with a moderate to high *E*-selectivity. Styrenes, allylsilanes, protected alcohols and amines are good partners as 1,1-disubstituted olefins [105–107]. This reaction has been exploited recently as part of a macrocyclization strategy in the epothilone series (Scheme 9.52) [108].



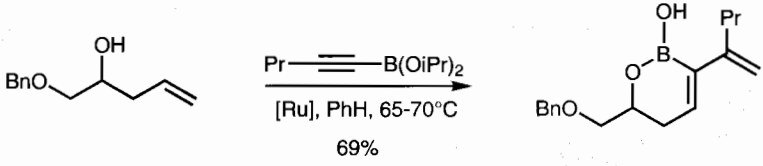


Scheme 9.51 Cyclic alkenyl- and dienylboronates via ring-closing metathesis.



Scheme 9.52 Synthesis of epothilone 490 using a ring-closing metathesis strategy.

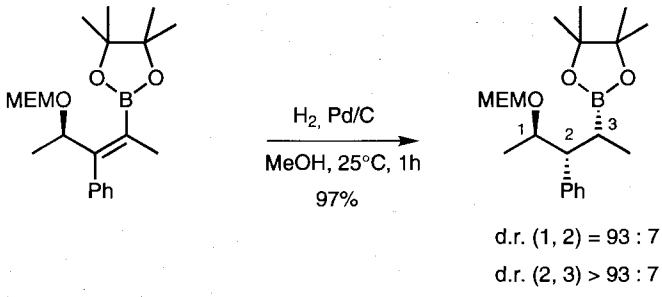
Notably, allylboronates can also be successfully used in a ruthenium-catalyzed cross-metathesis/allyboration sequence for the synthesis of homoallylic alcohols [109, 110]. Likewise, an unsaturated boronic ester annulation strategy with allylic and propargylic alcohols have found very elegant and useful applications in diversity-oriented organic synthesis (Scheme 9.53) [111].



Scheme 9.53 An alkynylboronic ester annulation.

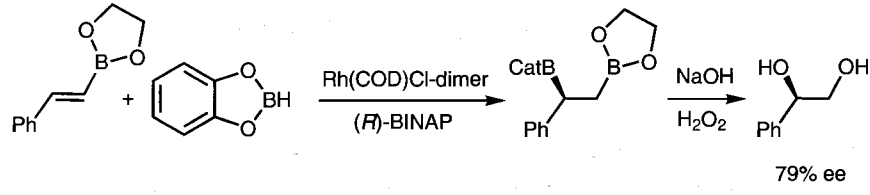
9.5
Miscellaneous Reactions

The carbon–carbon double bond of alkenylboronic esters was easily hydrogenated in the presence of palladium on charcoal to give the corresponding saturated species. With a tetrasubstituted substrate, the stereochemistry of two new adjacent centers was controlled (Scheme 9.54) [112]. Likewise, 1-alkynyldiisopropoxyboranes cleanly furnished (*Z*)-1-alkenylboronates over Lindlar catalyst in high stereoselectivity [113]. Asymmetric hydrogenation of 1-phenylethenylboronic ester has been carried out in the presence of $[Rh(cod)_2]BF_4$-(*R*)-BINAP. After oxidation, 1-phenylethanol was obtained with 80% ee [114].



Scheme 9.54 Diastereoselective hydrogenation of an alkenylboronic ester.

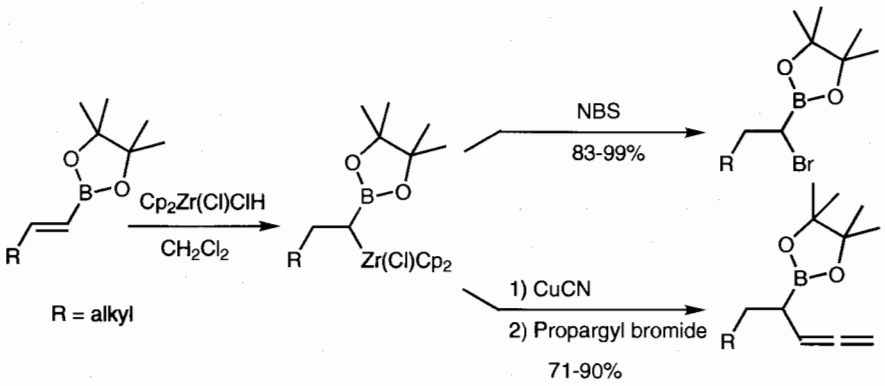
Catalytic hydroboration of alkenylboronic esters with catecholborane in the presence of rhodium complexes and various diphosphine ligands has afforded 1,2-diboronyl intermediates. Their subsequent oxidation gave the corresponding 1,2-diol with enantioselectivities of up to 79% ee (Scheme 9.55) [115].



Scheme 9.55 Rhodium-catalyzed enantioselective hydroboration of an alkenylboronate.

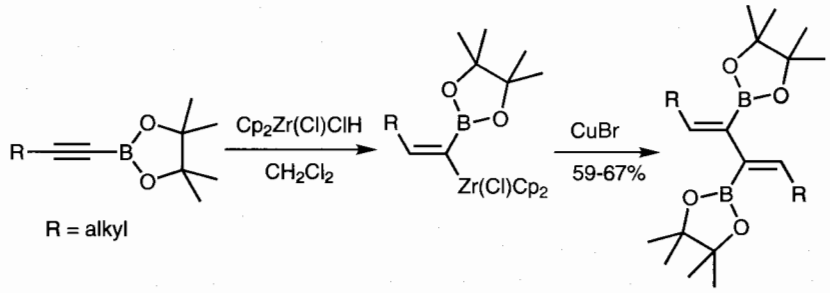
1,1-Boronozircono-alkanes and alkenes were obtained exclusively by hydrozirconation of 1-alkenyl- and l-alkynylboronates. These compounds reacted with *N*-halosuccinimides and were transmetallated into organocopper reagents, giving access to a range of new boronic esters (Scheme 9.56) [116]. A facile boron migration was observed during hydrozirconation of substituted alkenylboronates [117].

gem-Boronozirconocenes, obtained by hydrozirconation of 1-alkynylboronates with $HZrCp_2Cl$, provided homocoupled (1*E*,3*E*)-2,3-dibora-1,3-butadienes in good yields



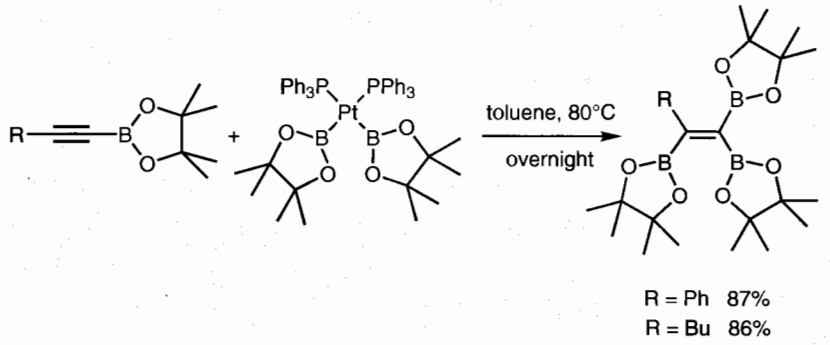
Scheme 9.56 Hydrozirconation of alkenylboronates and further transformations.

(Scheme 9.57) [118]. Cyclic 1-alkenyl-4-alkyl diboronates were available from the monoborylated 1,6-hexa- or heptadiyne and Negishi's reagent, Cp_2ZrCl_2/n-BuLi [119].



Scheme 9.57 Hydrozirconation of alkynylboronates and further homocoupling.

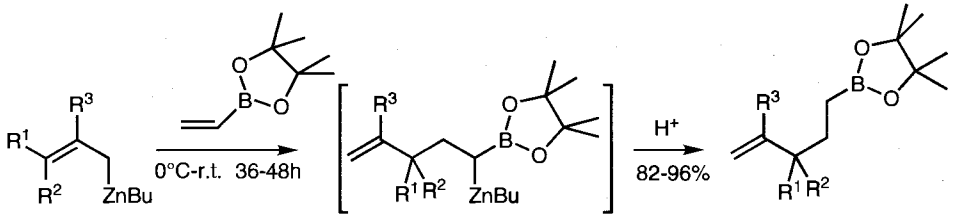
Platinum(0)-catalyzed diboration of 1-alkynylboronates with bis(pinacolato)diborane yielded the corresponding trisboronated alkene products in high yields (Scheme 9.58) [120]. Catalyzed diboration of styrylboronate esters in the presence of either $[Rh(PPh_3)_3Cl]$ or $[Rh(COE)_2(\mu\text{-}Cl)]_2$ and two equivalents of P(*o*-tol)$_3$ yielded predominantly the corresponding alkenyl tris(boronate) [121].



Scheme 9.58 Platinum(0)-catalyzed diboration of alkynylboronates.

An optically pure γ-silyloxyvinylboronate rearranged in the presence of thionyl chloride to afford the α-chloro-(*E*)-crotylboronate with a high level of chirality transfer [122]. Important applications of this rearrangement are in the synthesis of polyketide natural products and α-aminoboronates [123, 124]. A few examples of transition metal catalyzed isomerizations of alkenylboronates have been reported, providing allylboronates in good yields [125, 126].

The addition of allylic zinc reagents to alkenylboronates yielded various gem-zinc/boron species. Theoretical studies with density functional calculations of the reaction pathway revealed that the reaction proceeds via a zincio-ene reaction rather than a bora-Claisen rearrangement (Scheme 9.59) [127].



R^1, R^2, R^3= H, Me, Ph

Scheme 9.59 Regioselective allylzincation of a vinylboronate.

9.6 Conclusions

The aforementioned examples clearly show the utility of unsaturated boronic esters as key intermediates for the preparation of a wide range of organic molecules. In numerous cases, the regio- and stereoselectivity of the addition reactions can be controlled, in particular through a boron temporary tether. Further transformations of the boron–carbon bond into a new carbon–carbon or carbon–heteroatom bond offers crucial advantages compared with their other organometallic analogues. Many stimulating developments remain to be discovered, for example, through either metal-catalyzed reactions or one-pot multicomponent strategies.

9.7 References

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10
Organoboronic Acids and Organoborinic Acids as Brønsted–Lewis Acid Catalysts in Organic Synthesis

Kazuaki Ishihara

10.1
Introduction

Boron(III) compounds act as Lewis acids because there is an empty p-orbital on the boron atom. In general, classical boron Lewis acids such as BX_3 (X = F, Cl, Br, OCOR, OTf) are used stoichiometrically in organic transformations, and under anhydrous conditions because the presence of even a small amount of water causes rapid decomposition or deactivation of these promoters. To obviate some of these inherent problems, the potential of arylboron compounds, $Ar_nB(OH)_{n-3}$ (n = 1–3), bearing electron-withdrawing aromatic groups as a new class of boron catalysts has been demonstrated recently. For example, 3,5-$(CF_3)_2C_6H_3B(OH)_2$ is a thermally stable, water-tolerant acid that is commercially available. Arylboronic acids and diarylborinic acids act not only as Lewis acids but also as Brønsted acids. This chapter focuses on the organic transformations catalyzed by arylboronic acids and diarylborinic acids and the design of chiral arylboronate catalysts bearing electron-withdrawing aromatic groups [1].

10.2
Diarylborinic Acids

Diarylborinic acids bearing electron-withdrawing aromatic groups are effective catalysts for Mukaiyama aldol condensation and the subsequent selective dehydration of β-hydroxy carbonyl compounds [2]. Diarylborinic acids like $(C_6F_5)_2BOH$ and [3,5-$(CF_3)_2C_6H_3]_2BOH$, have a much higher catalytic activity in Mukaiyama aldol reactions than the corresponding arylboronic acids. Notably, small amounts of *E*-isomeric dehydrated product have been isolated in reactions catalyzed by diarylborinic acids. In contrast, no dehydrated products have been isolated in the presence of $(C_6F_5)_3B$, despite its extremely high catalytic activity (Equation 1).

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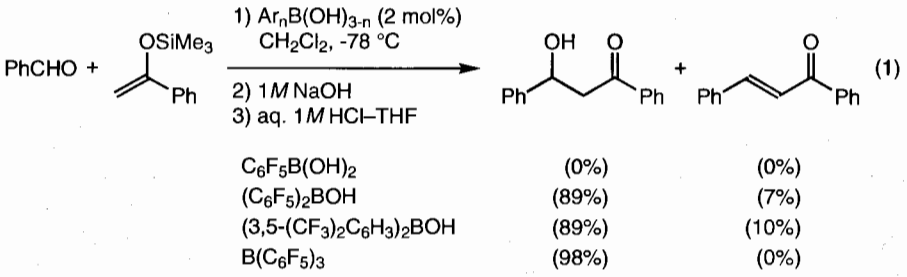
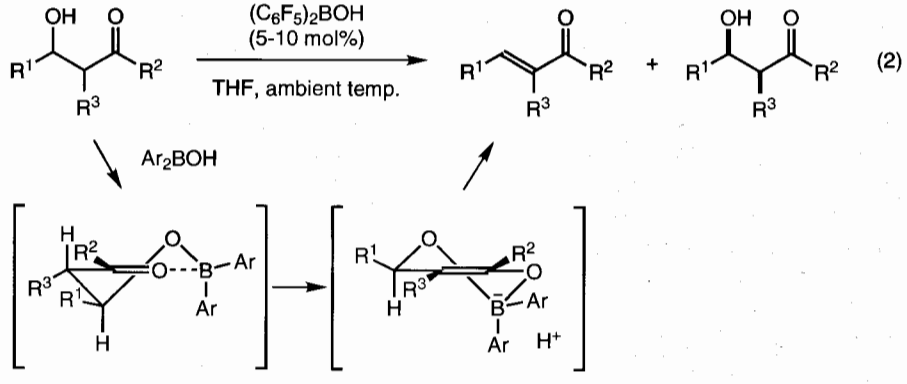
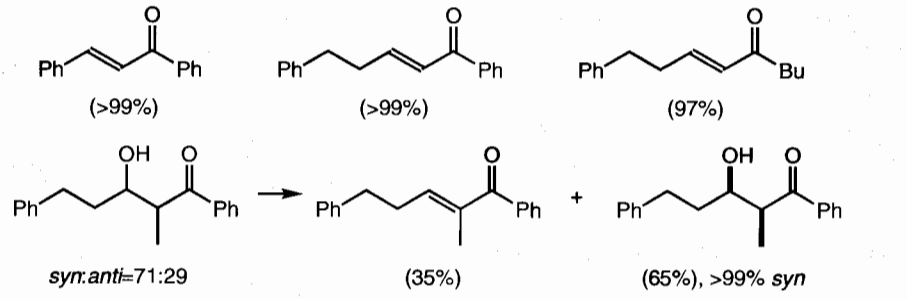


Significant features of these active borinic acid catalysts are that they are strong Lewis acids and possess a hydroxy group on the boron atom. Dehydration is strongly favored in THF. In most cases, the reaction proceeds smoothly, and α,β-enones are obtained in high yields as (*E*) isomers. In reactions of α-substituted-β-hydroxy carbonyl compounds, α,β-enones are preferentially obtained from anti aldols, while most of the syn aldols are recovered. This dehydration thus represents a useful and convenient method for isolating pure syn aldols from syn/anti isomeric mixtures (Equation 2).

According to the proposed mechanism, the β-hydroxy function reacts with the diarylborinic acid to give a cyclic intermediate that should be susceptible to dehydration. Subsequent transformation into α,β-enones occurs via an enolate intermediate

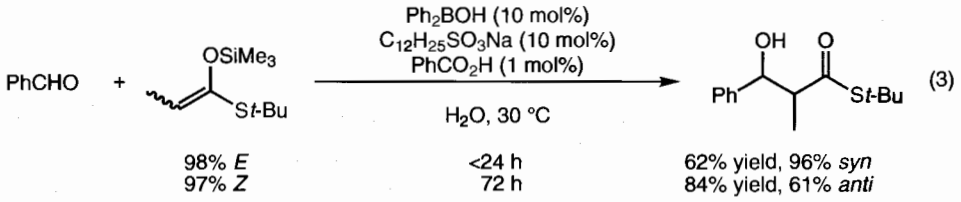


Examples



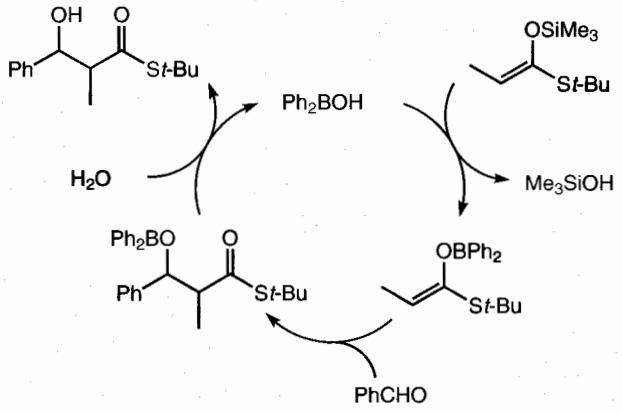
resulting from selective abstraction of a pseudo-axial α-proton perpendicular to the carbonyl face. Because of the pseudoaxial orientation of R^1, a cyclic intermediate formed from a syn aldol and a diarylborinic acid would be thermodynamically less stable than the cyclic intermediate from the anti aldol. Thus, dehydration to (*E*)-α,β-enones occurs selectively for anti aldols.

Kobayashi et al. have reported that Ph_2BOH is also an effective catalyst for the Mukaiyama aldol reaction in the presence of benzoic acid as a co-catalyst and sodium dodecyl sulfate as a surfactant (Equation 3) [3]. The use of water as a solvent is essential in this reaction. The reaction proceeds sluggishly in organic solvents such as dichloromethane and diethyl ether. Compared to water, much lower yields are obtained under neat conditions. High syn selectivity is observed when *Z*-enolates are used, while relatively low anti selectivity is observed with *E*-enolates.



(3)

The present reaction system can be explained by a mechanism involving a boron enolate as a reaction intermediate generated by Si–B exchange (Scheme 10.1). That the diastereoselection is reversed by using the stereoisomers of the silyl enolate supports this hypothesis because this type of reversal is commonly observed in the traditional boron enolate mechanism, which involves a chair-like six-membered transition-state. Furthermore, the trend that anti selectivity is poorer than syn selectivity in the reactions is also found in traditional boron enolate mediated aldol reactions. The mechanism is based on the hypothesis that Ph_2BOH can react with a silyl enolate to form the corresponding boron enolate under the conditions. When a *Z*-enolate is used, an aldehyde and the boron enolate react via a chair-like six-membered transi-

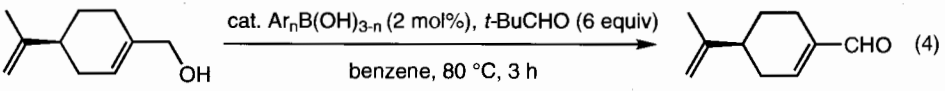


Scheme 10.1 Proposed boron enolate mechanism.

tion state to give the syn aldol product. The B–O bond of the initial aldol product is presumed to be cleaved easily by hydrolysis, and Ph_2BOH can be regenerated. In this mechanism, benzoic acid may accelerate the Si–B exchange step, which is thought to be a rate-determining step.

Oppenauer (OPP) oxidation is one of the most useful methods for transforming secondary alcohols into ketones. Functional groups such as carbon–carbon double and triple bonds, aldehydes, amino groups, halogens, or sulfur-containing groups are not affected by this reaction, which is a great advantage over many oxygen-transferring oxidation processes. For the selective oxidation of allylic alcohols in the presence of saturated alcohols, activated MnO_2 is still one of the most useful reagents, despite the large amount required. Ishihara and Yamamoto et al. have found that $(C_6F_5)_2BOH$ is a suitable OPP catalyst for primary and secondary allylic and benzylic alcohols [4]. $(C_6F_5)_2BOH$ is prepared from $(C_6F_5)_2BCl$ with aqueous 2 *M* HCl [5]. It is obtained as a white, microcrystalline solid that can be handled readily in air and is soluble in many organic solvents. $(C_6F_5)_2BOH$ is a stronger Lewis acid than $C_6F_5B(OH)_2$, although it is weaker than $B(C_6F_5)_3$ [6].

Several arylboron compounds bearing electron-withdrawing aromatic groups have been examined as catalysts for the OPP oxidation of (*S*)-perillyl alcohol (Equation 4). $(C_6F_5)_2BOH$ has a much higher catalytic activity than other diarylborinic acids. In contrast, the corresponding boronic acid $C_6F_5B(OH)_2$ is inert. The catalytic activities of these systems correlate with their expected Lewis acidities. Surprisingly, $B(C_6F_5)_3$ is also an active catalyst for the present oxidations, which can be explained by the in situ generation of $(C_6F_5)_2BOH$ as the actual catalyst from $B(C_6F_5)_3$. In fact, Ishihara and co-workers have ascertained by ^{19}F NMR analyses that $B(C_6F_5)_3$ gradually undergoes disproportionation to $(C_6F_5)_2BOH$ and pentafluorobenzene, and, finally, to $C_6F_5B(OH)_2$ under these reaction conditions. In general, triarylboranes and diarylborinic acids bearing electron-withdrawing substituents on their aryl groups are relatively stable in aqueous acidic solutions, but are unstable in neutral and basic aqueous solutions, where they undergo conversion into arylboronic acids and arenes.

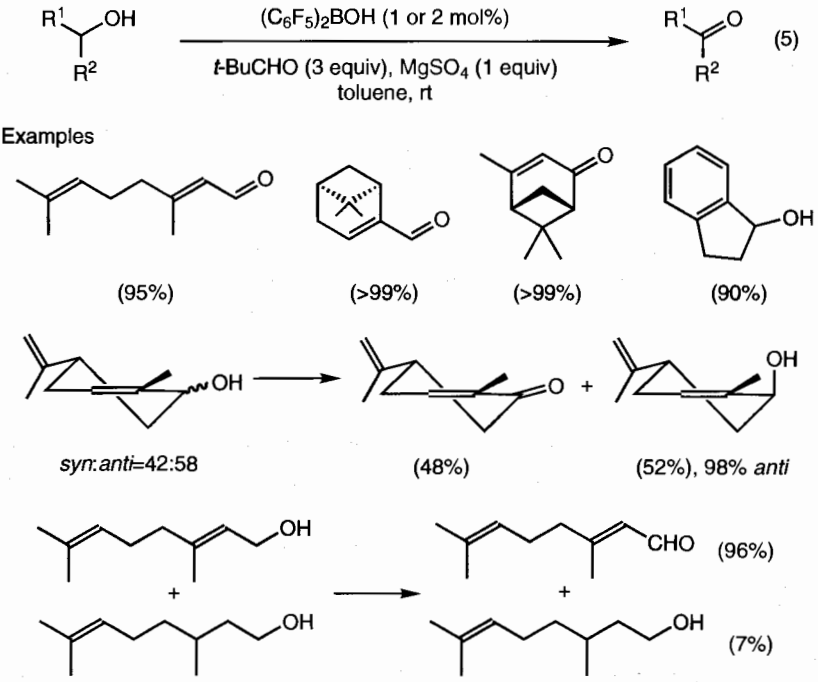


(4)

$C_6F_5B(OH)_2$: (0%); $(C_6F_5)_2BOH$: (>99%); $(C_6F_5)_3B$: (>99%)

The addition of magnesium sulfate efficiently prevents the inactivation of $(C_6F_5)_2BOH$ and hence promotes the oxidation (Equation 5). Removal of water by magnesium sulfate may prevent the hydrolysis of $(C_6F_5)_2BOH$ and promote the generation of a borinate species from $(C_6F_5)_2BOH$ and (*S*)-perillyl alcohol. Most allylic alcohols are oxidized to α,β-enals and α,β-enones in high yields. Primary and sterically less-hindered secondary benzylic alcohols are also oxidized efficiently in good yields. In the oxidation of a diastereomeric mixture of carveol (syn:anti = 42:58), the syn alcohol is stereoselectively oxidized, while the anti alcohol is recovered in 98% diastereomeric purity. This shows that the catalytic activity of $(C_6F_5)_2BOH$ is very sensitive to steric hindrance in the alcohols. In oxidations of equimolar mixtures of

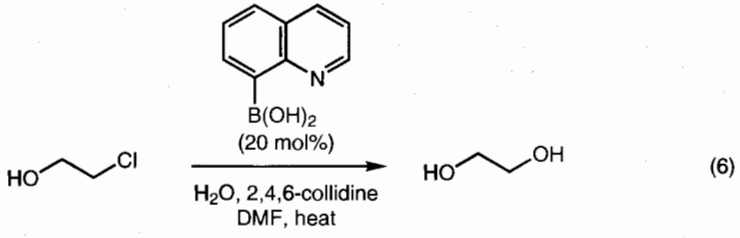
geraniol and β-citronellol, geranial is obtained in 96% yield and most of the β-citronellol is recovered unchanged.



10.3 Arylboronic Acids

Letsinger et al. have found that 8-quinolineboronic acid acts as a polyfunctional catalyst for hydrolysis of chloroethanol and 3-chloro-1-propanol in dimethylformamide (DMF) solutions containing water and 2,4,6-collidine (Equation 6) [7a]. In the absence of 8-quinolineboronic acid the chloroalcohols undergo slow solvolysis in DMF to products that are not glycols. Both water and ethylene glycol inhibit the catalytic reaction when present in high concentration. It is proposed that the boronic acid group in 8-quinolineboronic acid functions as a binding site for the chloroalcohol and that the nitrogen participates in the reaction as a basic or nucleophilic transforming site. Interestingly, *trans*-2-chloro-1-indanol is converted into *cis*-1,2-indandiol in good yield (Equation 7), while under the same conditions, the *cis*-2-chloro-1-indanol does not undergo carbon–chlorine fission when treated with 8-quinolineboronic acid (Equation 8) [7b]. These results are consistent with a reaction mechanism for the 8-quinolineboronic acid in which halogen is displaced by oxygen rather than by nitrogen. However, the nature of the activation and bonding of the nucleophilic oxygen cannot be ascertained from the data presently available. Attractive possibilities include: **1a**, in which the oxygen is located in a water molecule held between boron and nitrogen;

1b, in which the oxygen is covalently bound to boron and one hydrogen; and **1c**, in which the oxygen is covalently bound to two boron atoms.



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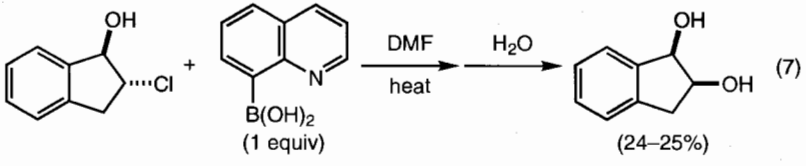
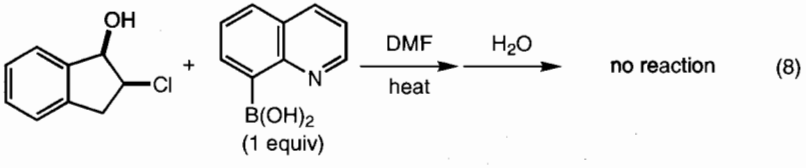


(7)



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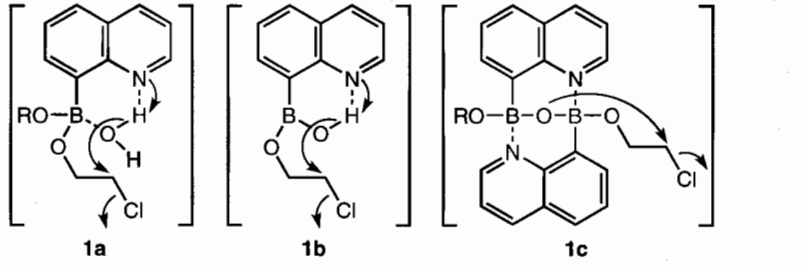
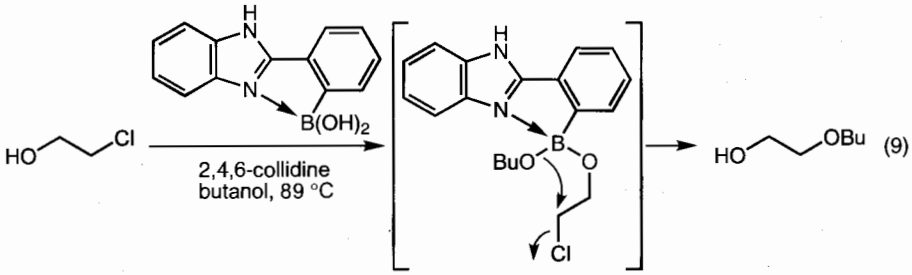
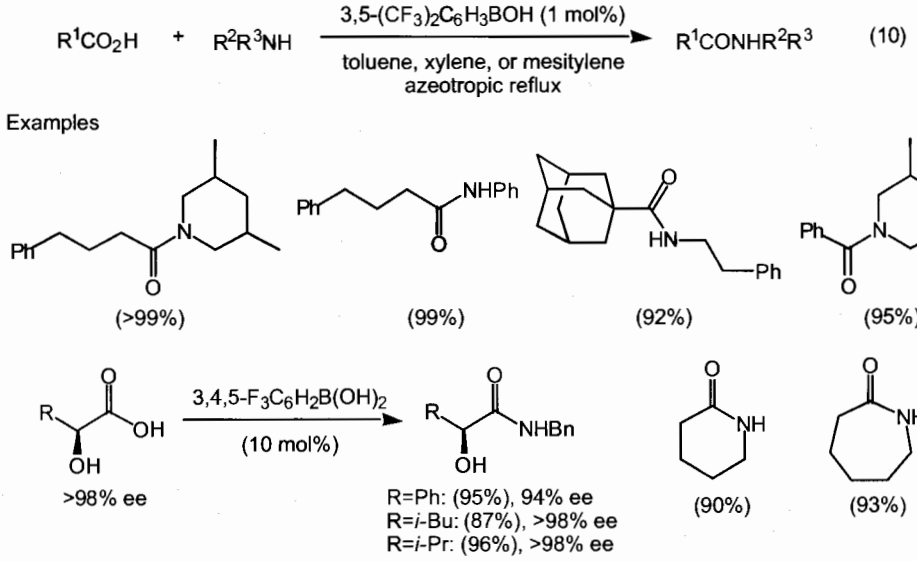


Letsinger et al. also found that 2-(2-boronophenyl)benzimidazole and 2-(2-boronobenzyl)benzimidazole serve as catalysts for the formation of ethers from chloroethanol in butanol solutions containing 2,4,6-collidine (Equation 9) [8]. They are much more effective in this regard than phenylboronic acid, 2-phenylimidazole or a mixture of these two substrates. It is proposed that the boronyl group binds the alcoholic substrates and holds them in a position favorable for reaction, while the nitrogen participates by increasing the nucleophilicity of oxygen joined to boron. Collidine acts as a transfer base to take up protons liberated in the reaction. In addition, Whiting et al. have recently reported on the preparation of 1-*N*,*N*-dimethylamino-8-bononaphthalene as a potential Lewis acid–Lewis base bifunctional catalysts [9].

Ishihara and Yamamoto et al. have found that arylboronic acids bearing electron-withdrawing aromatic groups, e.g. 3,4,5-$F_3C_6H_2B(OH)_2$ and 3,5-$(CF_3)_2C_6H_3B(OH)_2$, act as highly efficient catalysts in the amidation of carboxylic acids with amines [10].

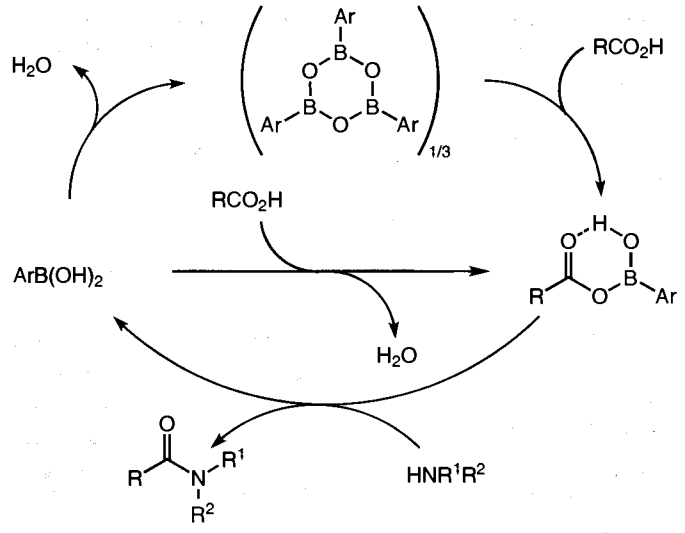


These catalysts are useful in the reactions of both primary and secondary amines with various carboxylic acids (Equation 10). Catalytic amidation of optically active aliphatic α-hydroxycarboxylic acids with benzylamine proceeds with no measurable loss (<2%) of enantiomeric purity under reflux conditions in toluene. Most amino acids are barely soluble in non-aqueous solvents. Nevertheless, their lactams can be prepared by the present technique under heterogeneous conditions. For example, when 6-aminocaproic acid and 1 mol% of the boron catalyst 3,4,5-$F_3C_6H_2B(OH)_2$ are suspended in refluxing xylene, the solid slowly dissolves and caprolactam is formed in 93% yield.



Scheme 10.2 depicts the proposed mechanism. In general, arylboronic acids contain varying amounts of cyclic trimeric anhydrides (boroxines).

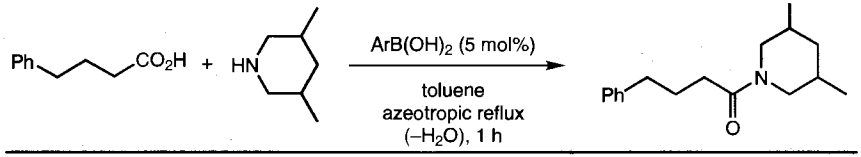
Ishihara and Yamamoto et al. have designed arylboronic acids bearing perfluorinated ponytails based on the direct coupling of fluoroalkyl iodides with halobenzene (Table 10.1). 3,5-$(C_{10}F_{21})_2C_6F_3B(OH)_2$ can be recovered easily in quantitative yield by extraction with perfluoromethylcyclohexane (the fluorous biphasic technique) [11]. Although 3,4,5-$F_3C_6H_2B(OH)_2$ and 3,5-$(CF_3)_2C_6H_3B(OH)_2$ are more active than 3,5-



Scheme 10.2 Proposed mechanism on the direct amide condensation catalyzed by arylboronic acids.

$(C_{10}F_{21})_2C_6F_3B(OH)_2$, they can not be recovered by extraction with any fluorous solvents.

Table 10.1 Catalytic activity and recovery of arylboronic acids for the direct amide condensation.



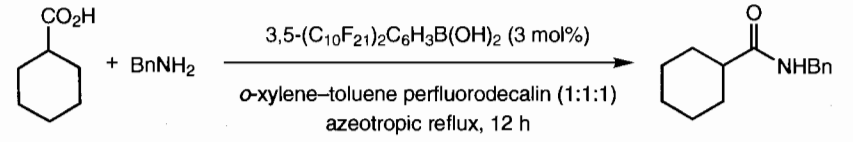
$ArB(OH)_2$	Yield of amide (%)[a]	Recovery of $ArB(OH)_2$ (%)[b]
$3,5\text{-}(CF_3)_2C_6H_3B(OH)_2$	59	0
$3,4,5\text{-}F_3C_6H_2B(OH)_2$	60	0
$3,5\text{-}(C_{10}F_{21})_2C_6H_3B(OH)_2$	47 (95)[c]	>99

[a] Isolated yield. [b] Extraction with perfluoromethylcyclohexane. [c] Yield after heating at azeotropic reflux for 15 h is indicated in parenthesis.

Based on the above results, the reuse of $3,5\text{-}(C_{10}F_{21})_2C_6H_3B(OH)_2$ has been examined for the direct amide condensation reaction of cyclohexanecarboxylic acid and benzylamine in a 1:1:1 mixture of *o*-xylene, toluene, and perfluorodecalin under azeotropic reflux conditions with removal of water for 12 h (Table 10.2 and Figure 10.1). Perfluorodecalin is not miscible with a non-fluorous solvent, toluene or *o*-xylene, even under reflux conditions. After completion of the reaction, the homogeneous solution is cooled to ambient temperature and separated in the bi-phase mode

of *o*-xylene–toluene/perfluorodecalin. The corresponding amide is obtained quantitatively from the organic phase. 3,5-$(C_{10}F_{21})_2C_6H_3B(OH)_2$ can be completely recovered from the fluorous phase and reused in the recyclable fluorous immobilized phase.

Table 10.2 Recovery and reuse of 3,5-$(C_{10}F_{21})_2C_6H_3B(OH)_2$ in the recyclable fluorous immobilized phase.



Cycle	1	2	3	4	5
Conversion (%)	>99	>99	>99	>99	>99

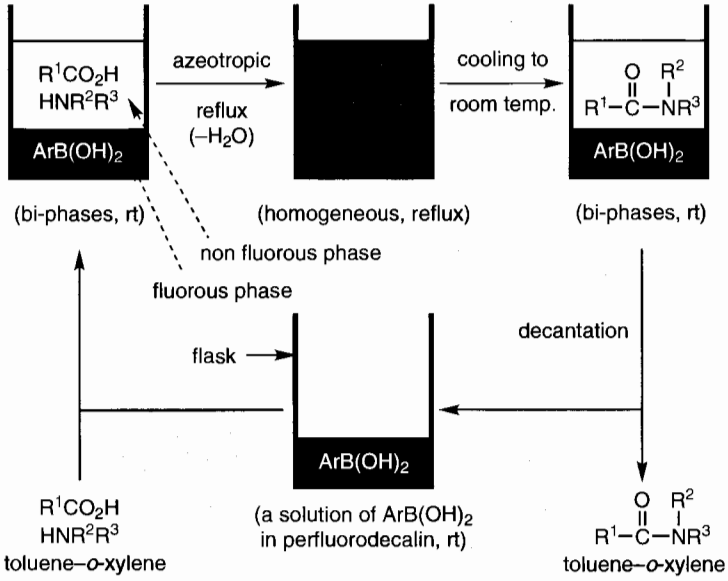
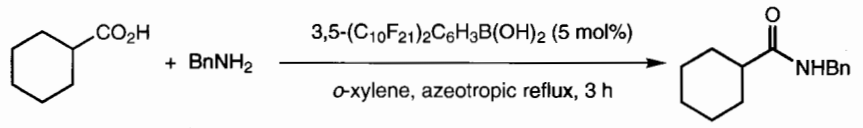


Figure 10.1 Recycle system of 3,5-$(C_{10}F_{21})_2C_6H_3B(OH)_2$ in the fluorous immobilized phase.

3,5-$(C_{10}F_{21})_2C_6H_3B(OH)_2$ is insoluble in toluene and *o*-xylene at room temperature even in the presence of carboxylic acids, amines, and amides, but is dissolved in the reaction solution under refluxing conditions. Ishihara and Yamamoto et al. have attempted to reuse 3,5-$(C_{10}F_{21})_2C_6H_3B(OH)_2$ (5 mol%) 10 times for the amide condensation reaction of cyclohexanecarboxylic acid with benzylamine without using any fluorous solvents (Table 10.3 and Figure 10.2). The reaction mixture, after heating at reflux with removal of water for 3 h, was allowed to stand at ambient temperature for 1 h to precipitate 3,5-$(C_{10}F_{21})_2C_6H_3B(OH)_2$. The liquid phase of the resultant mixture

was decanted and the residual solid catalyst was reused without isolation. The total isolated yield of the amide obtained after ten reaction cycles was 96%.

Table 10.3 Reuse of 3,5-$(C_{10}F_{21})_2C_6H_3B(OH)_2$ for the amide condensation of cyclohexane carboxylic acid with benzylamine.



Total (10 times): 96% isolated yield

Reuse of catalyst	1	2	3	4	5	6	7	8	9	10
Conversion (%)	>99	>99	>99	>99	99	>99	>99	>99	>99	>99

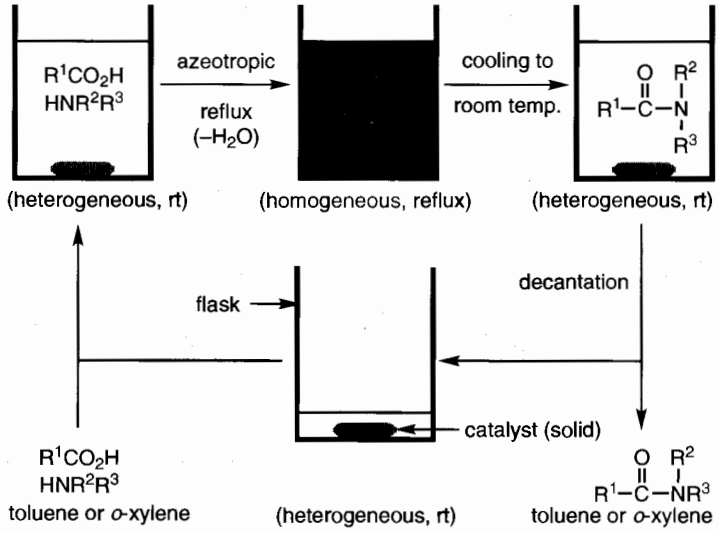
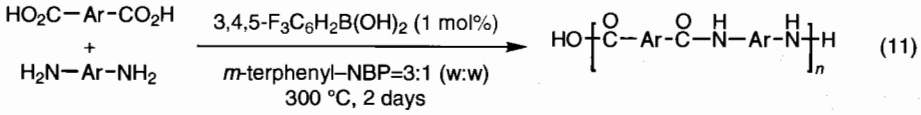


Figure 10.2 Recovery of 3,5-$(C_{10}F_{21})_2C_6H_3B(OH)_2$ by decantation and its reuse without isolation.

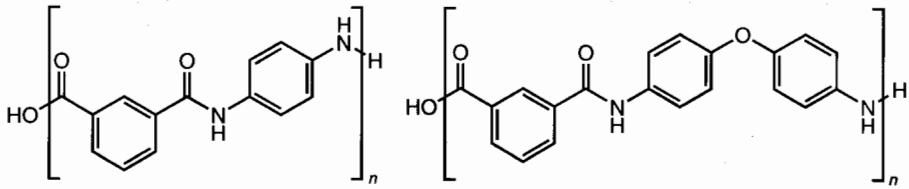
Polyamides are used in the production of synthetic fibers and engineering resins. Aromatic polyamides are particularly well known as high-performance polymers due to their excellent thermal, mechanical and chemical properties. Direct polycondensation that produces only a stoichiometric amount of water as a by-product is the ideal route, both environmentally and industrially. 3,4,5-$F_3C_6H_2B(OH)_2$ is a highly effective catalyst for the direct polycondensation to aramids, semiaromatic nylons, and polyimides (Equation 11) [10b]. However, it is difficult to obtain high molecular weight nylons using the present procedure. The desired high molecular weight aramid can be obtained quantitatively as a white solid by heating the reaction mixtures in the presence of only 1 mol% of 3,4,5-$F_3C_6H_2B(OH)_2$ in a mixed solvent of *m*-terphenyl and *N*-butyl-2-pyrrolidinone (NBP) at 300 °C (bath temp.) under a slow ar-

gon flow to remove water for two days. When the reaction is carried out without an argon flow, the reaction mixture gradually turns black.



(11)

Examples



(>99%), M_n=11500, M_w=28300 (95%), M_n=27400, M_w=173000

Pyridinium rings are electron deficient, and alkylation of the pyridine nitrogen allows for its ready attachment to a solid-phase material. Ishihara and Yamamoto and Wang et al. have found, independently, that 4-borono- and 3-borono-*N*-methylpyridinium iodides are effective as amide condensation catalysts [12]. Also, polystyrene-bound pyridinium boronic acid chloride is a useful, recoverable and reusable catalyst (Figure 10.3) [12b].

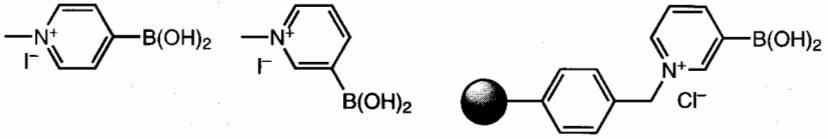
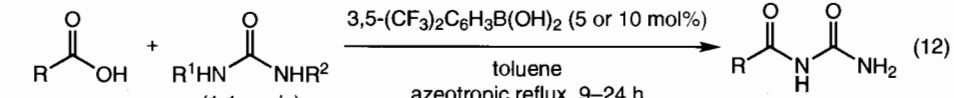


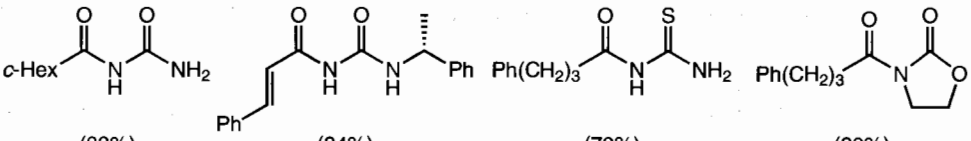
Figure 10.3 Pyridinium boronic acid salts as amide condensation catalysts.

3,4,5-$F_3C_6H_2B(OH)_2$ and 3,5-$(CF_3)_2C_6H_3B(OH)_2$ are highly effective as catalysts for the direct condensation of carboxylic acids with ureas to give *N*-acylureas, *N*,*N*′-diacyl-2-imidazolidones, and poly(*N*,*N*′-diacyl-2-imidazolidone)s (Equation 12) [13]. This system is believed to be the first catalytic synthesis of *N*-acylurea.



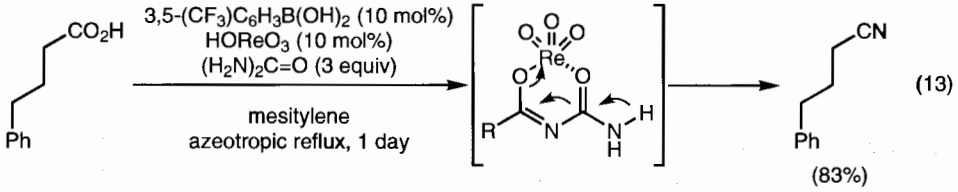
(12)

Examples



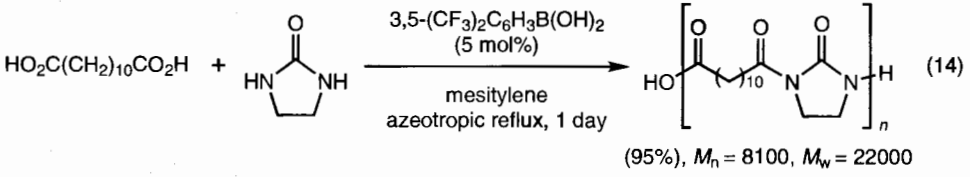
(82%) (84%) (72%) (80%)

Furthermore, a mixed catalyst, 3,5-$(CF_3)_2C_6H_3B(OH)_2$–$HOReO_3$ is effective for a one-pot synthesis of nitriles from the corresponding carboxylic acids and urea (Equation 13) [13]. Thus, 4-phenylbutyronitrile is obtained in good yield. This means that urea can be used as a synthetic equivalent of ammonia.



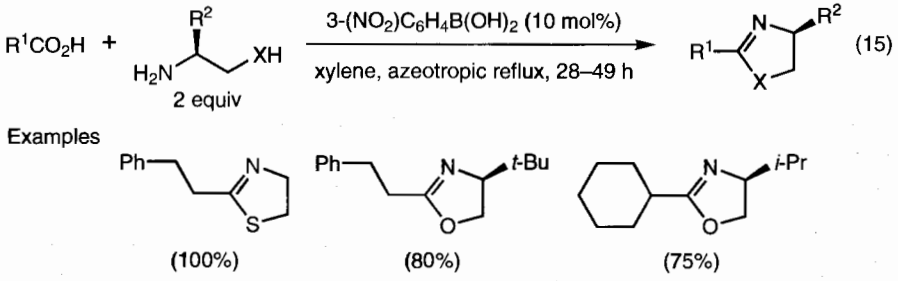
(13)

The present system has been applied to the direct polycondensation of α,ω-dicarboxylic acids with 2-imidazolidone. For example, poly[*N*,*N*′-(1,10-decanedicarboxyl)-2-imidazolidone] is directly synthesized by the reaction of 1,10-decanedicarboxylic acid with 2-imidazolidone in the presence of 5 mol% of 3,5-$(CF_3)_2C_6H_3B(OH)_2$ (Equation 14) [13].



(14)

Wipf et al. have reported that oxazolines and thiazolines can be synthesized by tandem condensation–cyclodehydration of carboxylic acids with amino alcohols and aminothiols in the presence of 3-$NO_2C_6H_4B(OH)_2$ in moderate to excellent yields (Equation 15) [14].



(15)

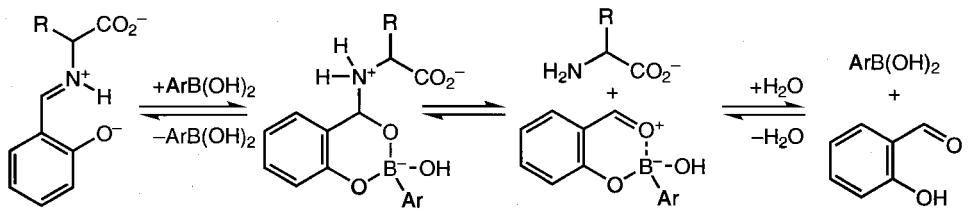
Tale et al. have reported that 3,4,5-$F_3C_6H_2B(OH)_2$ is an effective catalyst for the reduction of carboxylic acids with sodium borohydride (Equation 16) [15a] and azidation of carboxylic acids with sodium azides (Equation 17) [15b].

Hydrolysis of salicylaldehyde imines is catalyzed by boric acid, substituted arylboronic acids, and phenylborinic acid. Rao and Philipp have studied the effect of var-

$$RCO_2H + NaBH_4 \xrightarrow[THF,\ Na_2SO_4,\ rt,\ 10\ h]{3,4,5\text{-}F_3C_6H_2B(OH)_2\ (1\ mol\%)} RCH_2OH \quad (16)$$

$$RCO_2H + \underset{5\ equiv}{NaN_3} \xrightarrow[THF,\ Na_2SO_4,\ rt,\ 10\ h]{3,4,5\text{-}F_3C_6H_2B(OH)_2\ (1\ mol\%)} RCON_3 \quad (17)$$

ious substituted phenylboronic acids on the rate of hydrolysis at pH 6.0 [16]. The second-order rate constants, k_{cat}/K_m, are higher with arylboronic acids bearing electron-withdrawing substituents than those measured with phenylboronic acids bearing electron-donating substituents. The highest value obtained was 2.38 $M^{-1}\ s^{-1}$, using $3,5\text{-}(CF_3)_2C_6H_3B(OH)_2$, while the lowest was 0.09 $M^{-1}\ s^{-1}$, obtained with $4\text{-}MeC_6H_4B(OH)_2$. Arylboronic acids bearing electron-withdrawing substituents bind the imine more tightly than do boronic acids bearing electron-donating substituents. The effect of boric acid, phenylboronic acid, and phenylborinic acid on the hydrolysis of the same imine was also studied at pH 6.0. $PhB(OH)_2$ and $Ph_2B(OH)$ bind the imine more strongly than boric acid by factors of almost 25 and 4350, respectively (Scheme 10.3).



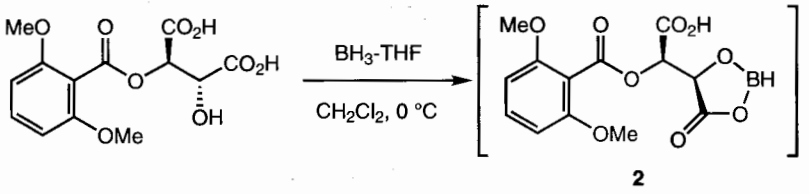
Scheme 10.3 Hydrolysis of salicylaldehyde imines catalyzed by $ArB(OH)_2$.

10.4
Chiral Boronate Lewis Acids

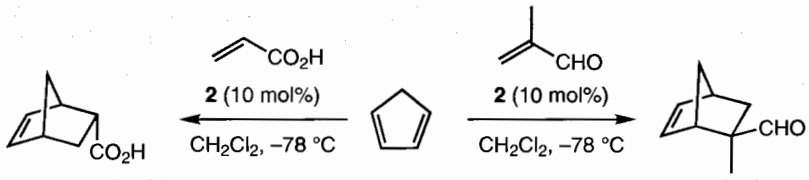
10.4.1
Enantioselective Carbo Diels–Alder Reactions

Yamamoto et al. have found that the action of a controlled amount of diborane on a carboxylic acid leads to an (acyloxy)borane $RCO_2BR'_2$, which behaves as a Lewis acid [17]. The chiral (acyloxy)borane (CAB) complex **2** that is formed in situ from monoacyl tartaric acid and diborane is an excellent asymmetric catalyst (Equation 18) for the Diels–Alder reaction of cyclopentadiene with acrylic acid [17] or methacrolein (Equation 19) [18].

The reaction with acrylic acid deserves special attention, since it is usually not a good component in Diels–Alder reactions. The fact that the reaction proceeds cat-



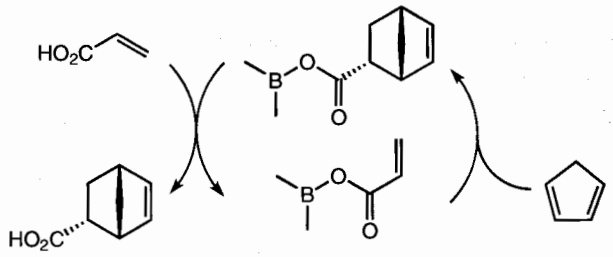
(18)



(19)

78% ee endo, 96% endo

96% ee exo, 89% exo

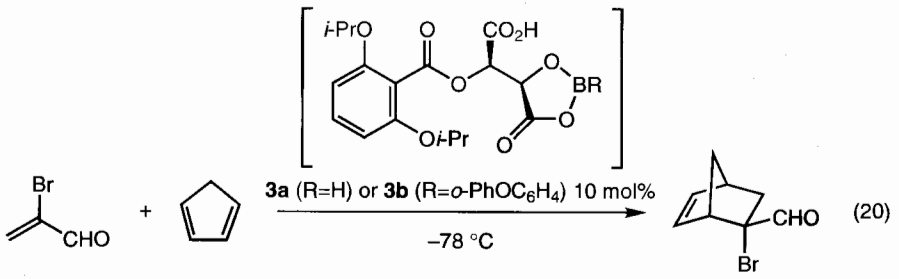


Scheme 10.4 Catalytic cycle of the Diels–Alder reaction of acrylic acid catalyzed by **2**.

alytically and with high ee indicates the facile exchange of the (acyloxy)borane of the cycloadduct with the carboxylic group of unreacted acrylic acid, while the monoacylated tartaric acid remains bound to boron (Scheme 10.4).

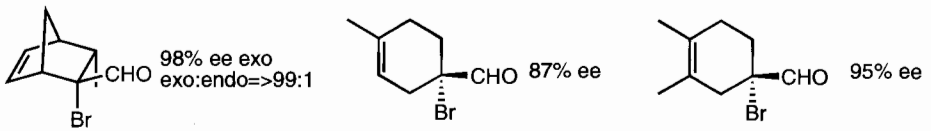
The CAB process is quite general for simple dienes and aldehydes. The α-substituent on the dienophile increases the enantioselectivity (acrolein vs methacrolein). When there is a β-substitution in the dienophile, as in crotonaldehyde, the cycloadduct is nearly racemic. Conversely, for a substrate with substituents at both α- and β-positions, high ees are observed, as with 2-methylcrotonaldehyde and cyclopentadiene (90% ee, exo:endo = 97:3). α-Bromoacrolein is a useful dienophile in the Diels–Alder process because of the exceptional synthetic versatility of its resulting adducts: e.g., an important intermediate for prostaglandin synthesis [19a]. In the presence of 10 mol% of **3a**, α-bromoacrolein and cyclopentadiene in dichloromethane undergo a smooth Diels–Alder reaction to give the (*S*)-bromoaldehyde cycloadduct in quantitative yield, 95% ee and 94:6 (exo:endo CHO) diastereoselectivity (Equation 20). Similar results are obtained for the catalyst **3b** in propionitrile. Other examples are listed below [20].

Hawkins et al. have reported a simple, efficient catalyst for the Diels–Alder reaction based on a chiral alkyldichloroborane (**4**, Equation 21) [21]. A molecular complex between methyl crotonate and the chiral catalyst has been isolated for the first time.

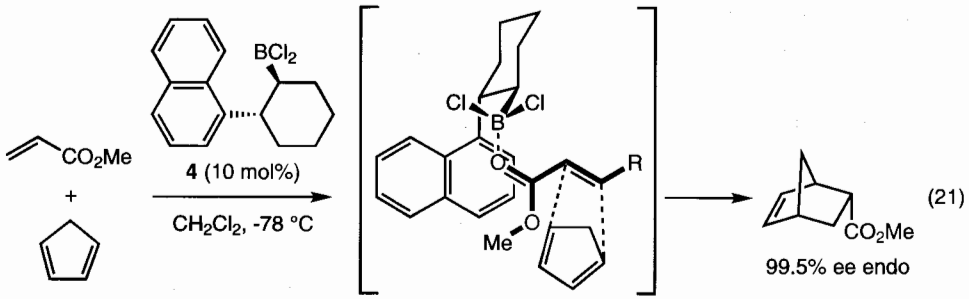


3a: 95% ee exo, 94% exo; **3b**: 98% ee exo, 94% exo

Other Examples (Use of **3a**)



A crystal structure study of the complex allowed the authors to propose a model to predict the approach of the diene on one of the faces of the methyl crotonate, since the other face is inaccessible due to π–π donor–acceptor interactions involving the naphthyl unit. This secondary attractive substrate-catalyst interaction is key to the stereocontrol.



99.5% ee endo

A similar effect has been reported by Corey et al. using tryptophan-derived oxazaborolidinone (OXB) catalysts of type 5 (Equation 22) [19], which are especially efficient in asymmetric catalysis of the cycloaddition between 2-bromoacrolein and various dienes (>90–95% ee). Attractive interactions between the indolyl moiety and the π-acidic dienophile protect one face of the dienophile. This effect is well supported by the discovery that replacement of the indole group by a cyclohexyl or an isopropyl group gives the cycloadduct with an opposite configuration (70% ee).

OXB catalyst **6a** derived from *N*-tosyl (α*S*,β*R*)-β-methyltryptophan catalyzes the Diels–Alder reaction of 2-bromoacrolein and furan with 92% ee, leading to an efficient synthesis of numerous chiral 7-oxabicyclo[2.2.1]heptene derivatives (Figure 10.4) [22]. Interestingly, the analog **6a** of catalyst **5b**, which lacks the β-methyl group, is not as effective in catalyzing the formation of Diels–Alder product.

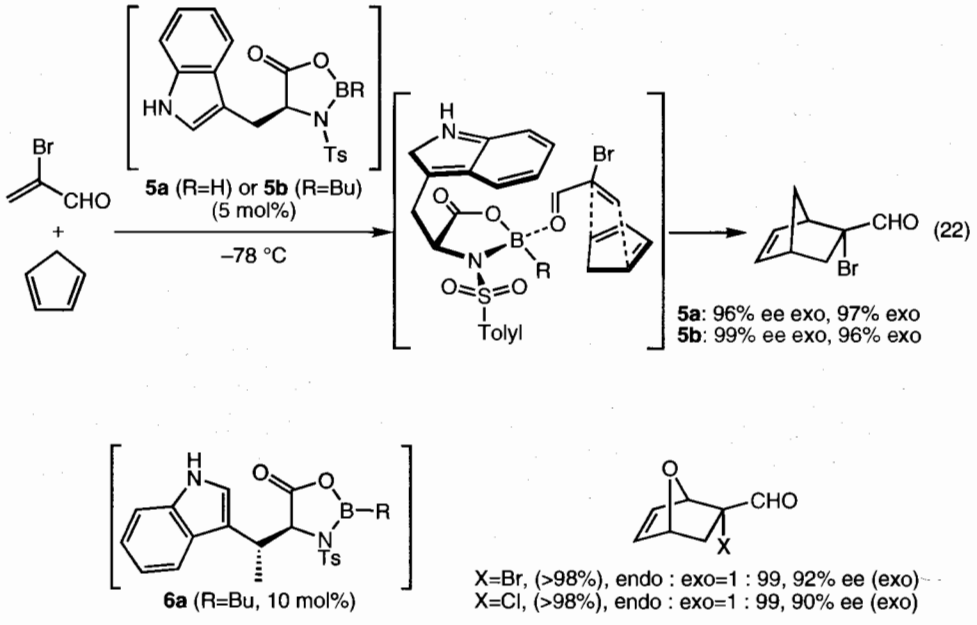
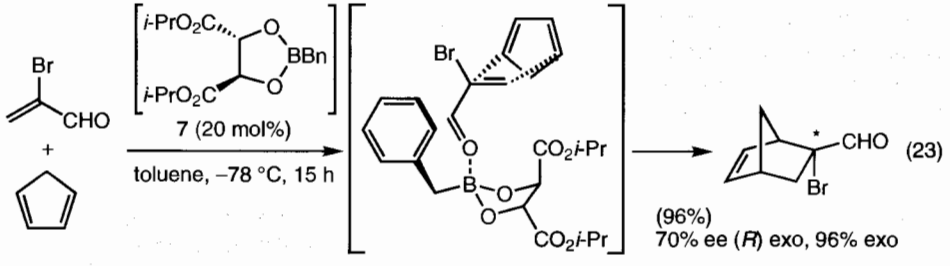


Figure 10.4 Diels–Alder reaction of 2-haloacrolein and furan catalyzed by **6a**.

Chiral tartrate-derived dioxaborolane **7** has been used to effect enantioselective Diels–Alder reactions of α-bromoacrolein and cyclopentadiene (Equation 23) [23]. The two tartrate ester units prefer to occupy the axial position with respect to the dioxaborolane unit. It is thought that the stabilized dipole–dipole interaction between the carbonyl carbon (δ^+) and the proximate ester carbonyl oxygen, together with the attractive interaction of the π-basic benzyl ring and the π-acidic dienophile in the *s-cis* conformation, locks the dienophile in the *s-cis* conformation. Approach of the diene from the less sterically hindered side (opposite the aryl ring) gives the cycloadducts in good enantioselectivity.



Ishihara and Yamamoto et al. have found that chiral boron ate complexes prepared from chiral tetraols and BH_3·THF or $B(OR)_3$ give new catalysts [Brønsted acid-assisted chiral Lewis acids (BLA)] in enantioselective synthesis, which achieve selectivity

through a double effect of intramolecular hydrogen-bonding interaction and attractive π–π donor–acceptor interaction by a hydroxy aromatic group in the transition state (Figure 10.5) [24a]. (*R*)-3,3′-bis(2-Hydroxyphenyl)-2,2′-dihydroxy-1,1′-binaphthyl reacts with $B(OMe)_3$ in dichloromethane at reflux with removal of methanol to give a white precipitate corresponding to **8**. High enantioselectivity and exo selectivity are obtained for Diels–Alder cycloadditions of α-substituted α,β-enals with dienes in the presence of **8**.

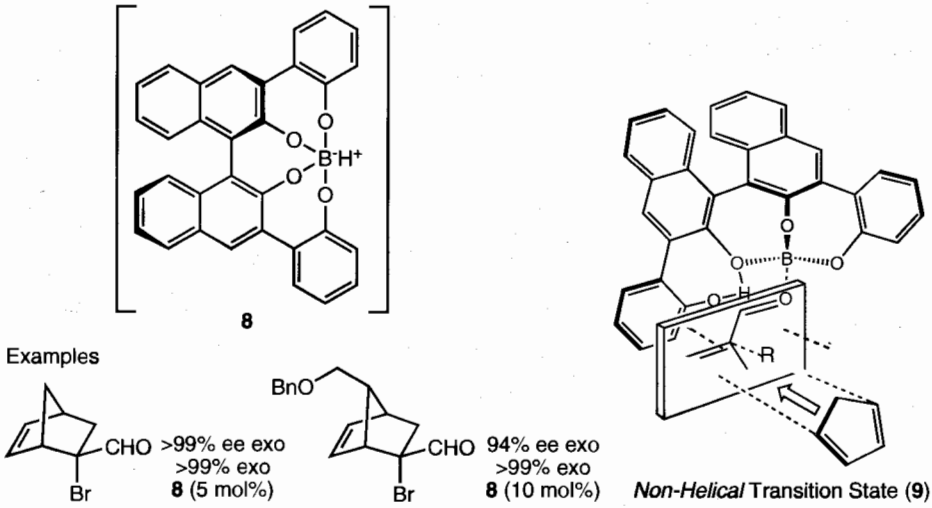
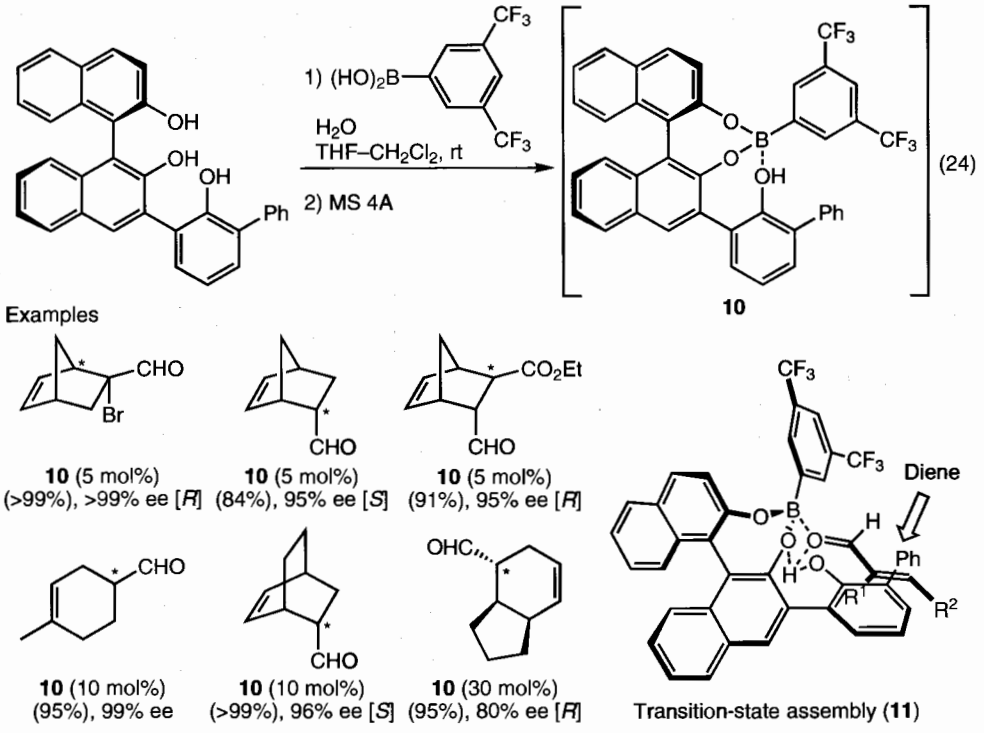


Figure 10.5 BLA-catalyzed enantioselective Diels–Alder reaction.

The absolute stereochemical course in the Diels–Alder reaction can be easily understood in terms of the most favorable transition-state assembly **9**, in which an attractive donor–acceptor interaction favors coordination of the dienophile at the face of boron that is cis to the 2-hydroxyphenyl substituent (Figure 10.5). The conformation of the α,β-enal shows an *s-trans* preference. Coordination of a proton of the 2-hydroxyphenyl group with an oxygen of the adjacent B–O bond in **9** plays an important role in asymmetric induction; this hydrogen-bonding interaction via Brønsted acid would cause the Lewis acidity of boron and the π-basicity of the phenoxy moiety to increase, thus stabilizing transition state **9**. The π-basic phenoxy moiety and the π-acidic dienophile could then assume a parallel orientation at the ideal separation (3 Å) for π donor–acceptor interactions. In this conformation, the hydroxyphenyl group blocks the *si*-face of the dienophile, leaving the *re*-face open to approach by the diene.

The use of arylboronic acids with electron-withdrawing substituents such as 3,5-$(CF_3)_2C_6H_3B(OH)_2$ in the preparation of BLA greatly enhances its catalytic activity and asymmetry-inducing ability. Ishihara and Yamamoto et al. have developed a more practical BLA (**10**), which has a greater catalytic activity in the enantioselective cycloaddition of both α-substituted and α-unsubstituted α,β-enals with various dienes (Equation 24) [24b,d]. Notably, the presence of a Brønsted acid in BLA catalysts clearly

accelerates the cycloaddition. The high enantioselectivity and stereochemical results attained in this reaction can be understood in terms of the transition-state model **11**.



BLA **10** is prepared from a chiral triol and monomeric 3,5-$(CF_3)_2C_6H_3B(OH)_2$ in the presence of powdered MS 4Å in dichloromethane–THF. Although molecular sieves are essential for dehydration, they may facilitate the aryloxy-ligand exchange reaction. Arylboronic acids usually exist as a mixture of monomer, trimer, and oligomer. To prevent oligomerization of 3,5-$(CF_3)_2C_6H_3B(OH)_2$ in preparing the catalyst, THF is needed as an additive (Figure 10.6) [24d].

The absolute stereochemical course in the Diels–Alder reaction catalyzed by **10** is opposite that catalyzed by **8**. This means that the presence of the *B*-aryl group greatly affects the asymmetric induction of BLAs prepared from chiral ligands with the same absolute configuration. In fact, the use of BLAs **8** and **12** prepared from the common chiral tetraol in the Diels–Alder reaction give an opposite enantiomer with high selectivity (Equation 25 vs. 26 respectively) [24d].

Diarylborinic acids are stronger Lewis acids than the corresponding boronic acids [25]. Ishihara and Yamamoto et al. have designed BLA **13**, which is prepared from $[3,5\text{-}(CF_3)_2C_6H_3]_2B(OH)$ and a chiral triol in dichloromethane in the presence of MS 4A (activated powder) at room temperature [24d]. Diels–Alder reaction of cyclopentadiene and various α,β-enals proceeds smoothly in the presence of 5 mol% of **13**, and good enantioselectivities have been observed for the exo adducts (Figure 10.7).

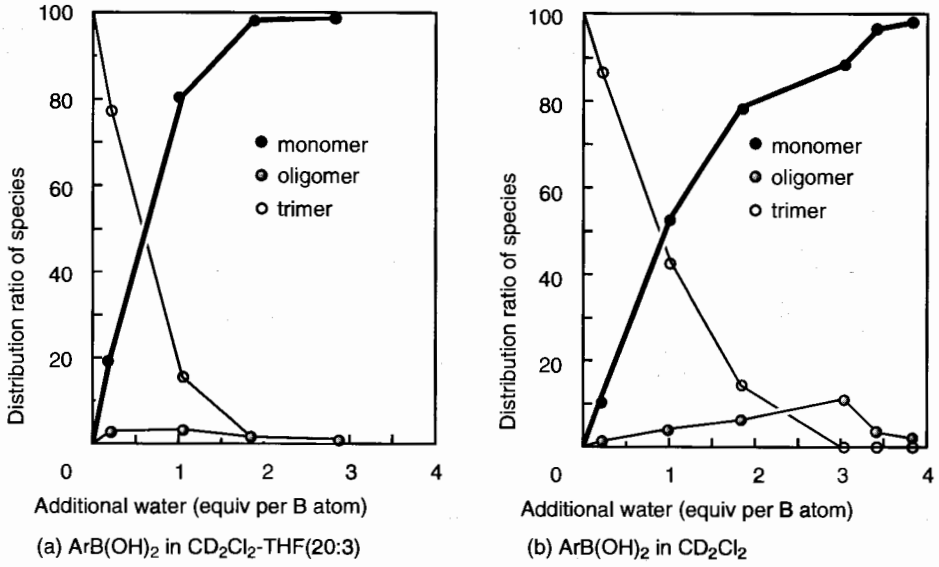
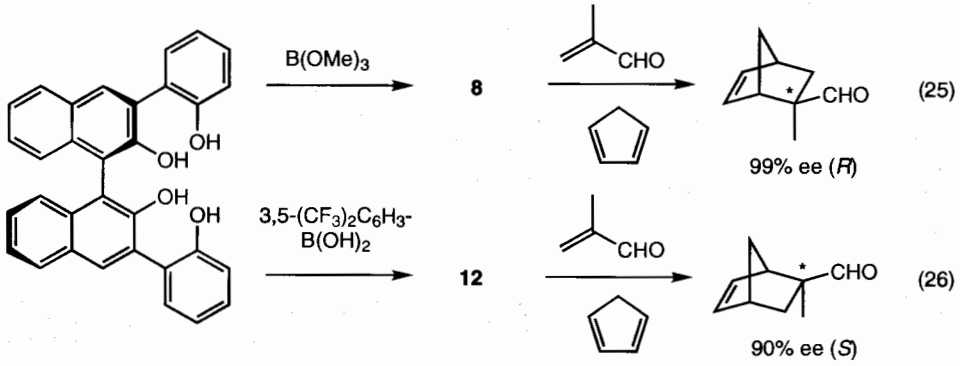
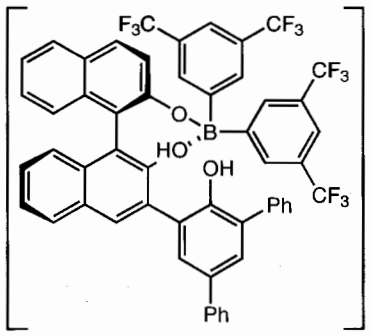


Figure 10.6 Plot of the distribution of species in a solution of $3,5\text{-}(CF_3)_2C_6H_3B(OH)_2$ versus additional water.

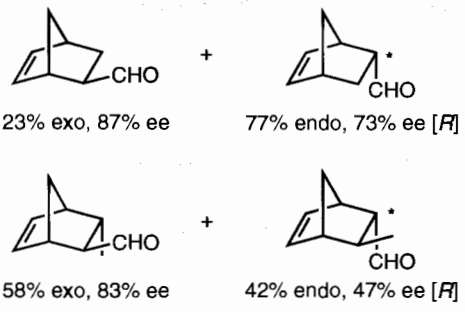


Ishihara and Yamamoto et al. have reported not only the first example of an enantioselective reaction of dienes, which have prochiral centers, and acetylenic aldehydes catalyzed by **3c** [R = $3,5\text{-}(CF_3)_2C_6H_3$], **8**, and **10** (Equation 27), but also an ab initio study that supports the predominance of an exo-transition structure, thus clarifying the origin of the enantioselectivity observed upon catalysis [24c]. The reaction of cyclic dienes and acetylenic dienophiles catalyzed by **10** proceeded with good enan-



13

Examples

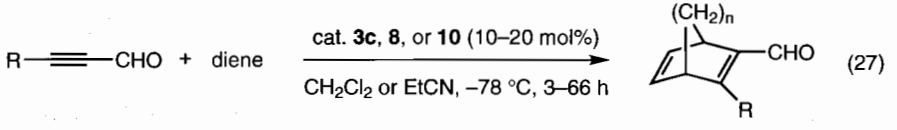


23% exo, 87% ee — 77% endo, 73% ee [*R*]

58% exo, 83% ee — 42% endo, 47% ee [*R*]

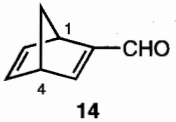
Figure 10.7 Diels–Alder reaction catalyzed by 5 mol% of **13**.

tioselectivity and conversion, although the use of **3c** or **8** gave higher enantioselectivity in some cases. Absolute configurations of the adducts with **3c** and **8** are opposite to those with **10**. This inversion of absolute stereochemistry is analogous to the reaction of dienes and α,β-enals [24d]. Optically active norbornadiene products **14** and **15** are key intermediates for the synthesis of biologically active analogues of the prostaglandin endoperoxides PGH_2 and PGG_2 [26] and β-santalol [27]. 3-Iodopropynal is an outstanding dienophile in these catalytic processes, not only because of the observed enantioselectivity and reactivity but also because of the synthetic versatility of the resulting adducts.



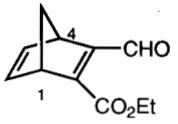
(27)

Examples

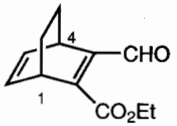


14

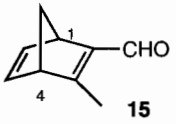
3c: (63%), 88% ee (1*R*,4*S*)-(–)
10: (<28%), 95% ee (1*S*,4*R*)-(+)



3c: (99%), 78% ee (1*R*,4*S*)-(+)
8: (97%), 95% ee (1*R*,4*S*)-(+)
10: (98%), 63% ee (1*S*,4*R*)-(–)

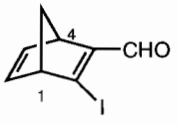


3c: (18%), 86% ee (–)
8: (81%), 84% ee (–)
10: (54%), 34% ee (+)



15

3c: (34%), 89% ee (1*R*,4*S*)-(+)



8: (72%), 85% ee (1*S*,4*R*)-(–)
10: (85%), 81% ee (1*R*,4*S*)-(+)

The absolute stereochemical selectivities attained in these reactions can be explained in terms of the anti-exo-transition-state models **16**–**18**, which are analogous to those previously proposed for the reaction of dienes and olefinic dienophiles (Figure 10.8) [20b, 24d]. These transition state models are based on the following assumptions: (1) the substituent in the chiral ligand blocks the same enantiofacial side of the carbonyl in the Diels–Alder reactions of both acetylenic and olefinic aldehydes; (2) exo-transition structures predominate; and (3) anti coordination of the bulky chiral Lewis acid to the carbonyl is preferred in the transition state.

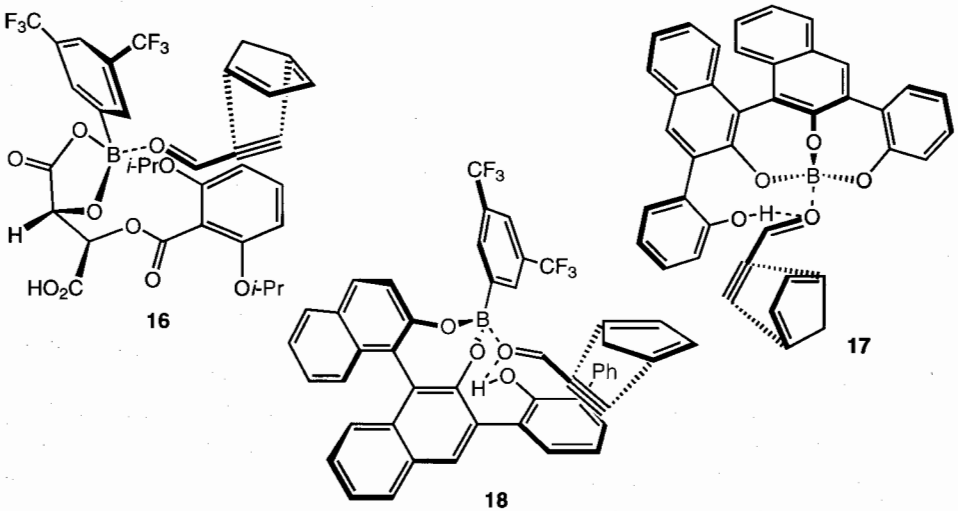
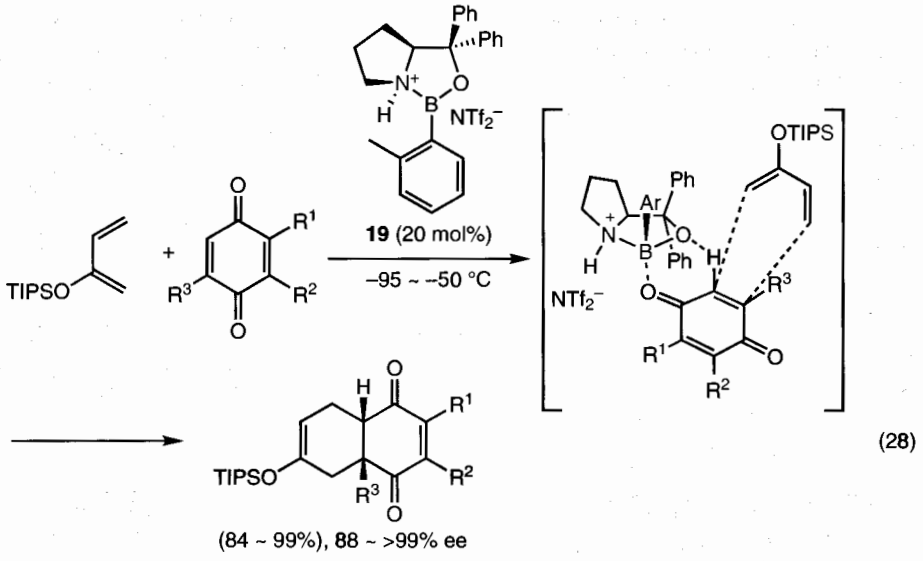


Figure 10.8 Proposed anti-exo-transition structures for the cycloaddition of cyclopentadiene and propynal.

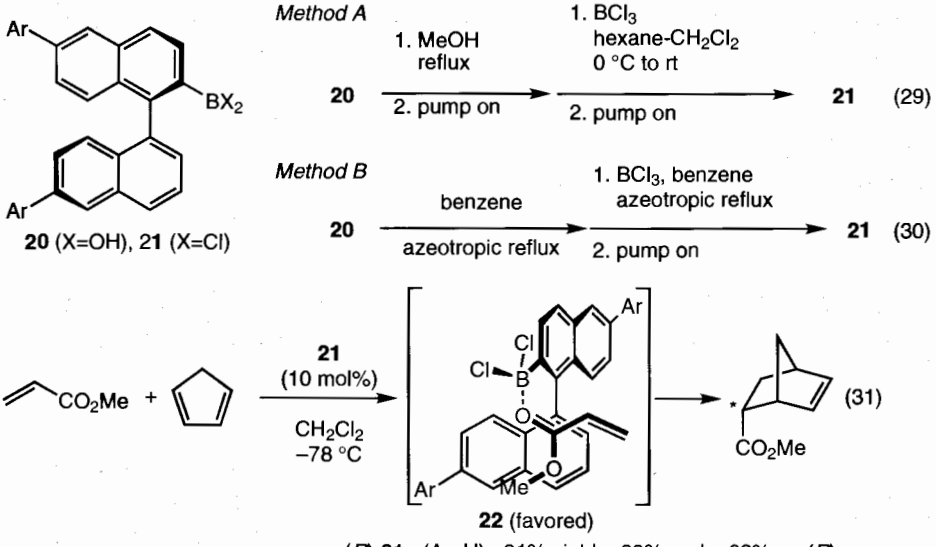
Corey et al. have found that chiral cationic oxaborolidinium triflylimide **19** is a useful and potent catalyst for promoting a wide variety of highly enantioselective Diels–Alder reactions of unsymmetrical 1,4-benzoquinones and 1,3-dienes (Equation 28) [28]. Not only enantioselectivity but also regio selectivity (i.e., only one of the two possible modes of coupling the ends of the diene and dienophile) and site-selectivity (i.e., reaction at only one of the two C=C subunits of the quinone) have been achieved in this catalysis.

Chiral alkyldihaloboranes are one of the most powerful chiral Lewis acids. However, in general, since alkyldihaloboranes readily decompose into alkanes or alkenes by protonolysis or β-hydride elimination, it is difficult to recover them as alkylboronic acids quantitatively. Aryldichloroboranes are relatively more stable and can be reused as the corresponding boronic acids. Ishihara and Yamamoto et al. have developed chiral aryldichloroboranes **21** bearing binaphthyl skeletons with axial chirality as asymmetric catalysts for the Diels–Alder reaction of dienes and α,β-unsaturated esters (Equation 31) [29]. (*R*)-2-Dihydroxyboryl-1,1′-binaphthyl (**20**) can be synthesized from (*R*)-binaphthol in several steps [25]. The synthesis of racemic **20a** has also been reported by Kaufmann et al. [30]. Compound **20** has been converted into **21** by two dif-



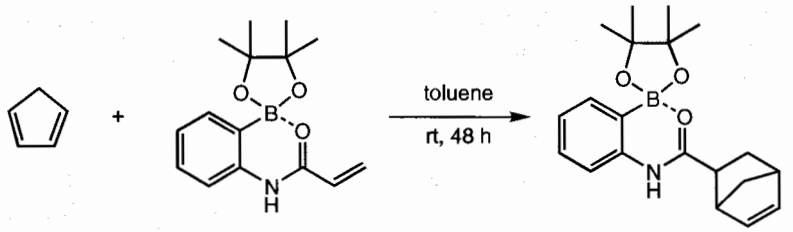
(28)

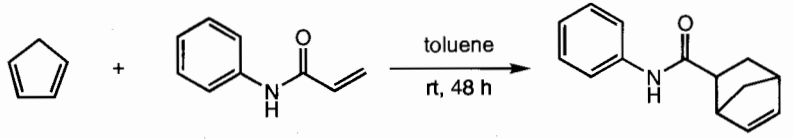
ferent methods: (1) via exchange of the methanol boronate with trichloroborane (Method A, Equation 29), and (2) via exchange of the boronic anhydrides with trichloroborane (Method B, Equation 30). The absolute configuration of the major endo adduct is consistent with the naphthyl group shielding the *re* face of the coordinated methyl acrylate, which leads to attack by cyclopentadiene at the *si* face, as shown in complex **22** (Equation 31). Increased enantioselectivity with the use of **21b** can be easily understood in terms of steric repulsion between the alkene and mesityl groups.



(*R*)-**21a** (Ar=H): 91% yield, >99% endo, 62% ee (*R*)
(*R*)-**21b** (Ar=2,4,6-$Me_3C_6H_2$): 92% yield, >99% endo, 73% ee (*R*)

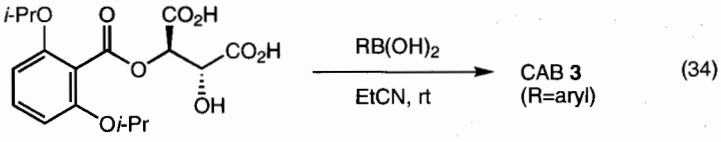
Dialkoxyboronic esters are a priori very weak Lewis acids. Diels–Alder reaction of an *ortho*-boronoanilide dienophile with cyclopentadiene proceeds faster than both its para isomer and the unsubstituted derivative, thereby confirming that self-activation by internal coordination is operative with *ortho*-boronoanilide (Equation 32 vs. 33). However, the level of 1,8-stereoselection observed in the Diels–Alder reaction of chiral boronic ester derivatives is only minimal (up to 18% de) [31].

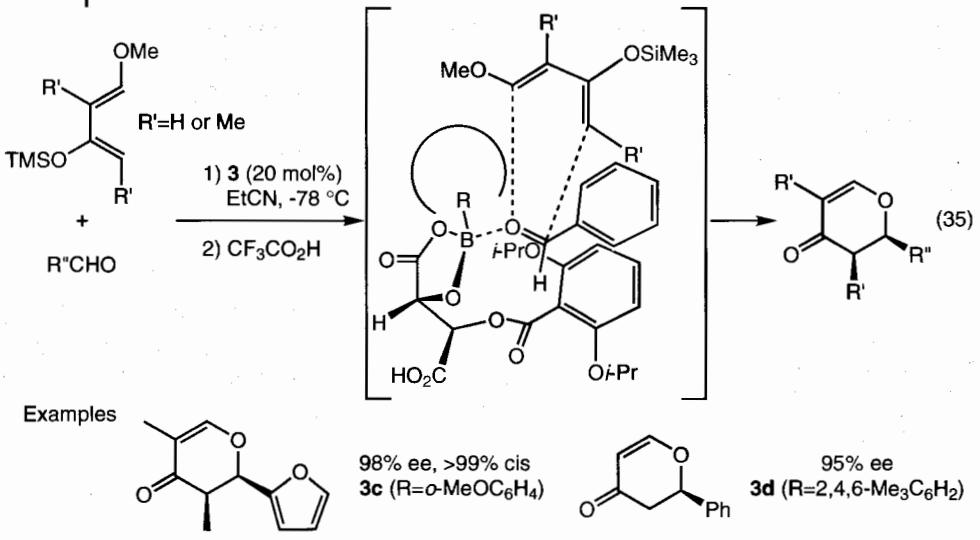




10.4.2
Enantioselective Hetero-Diels–Alder Reactions

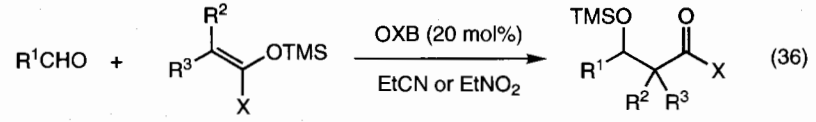
Ishihara and Yamamoto et al. have developed a stable complex **3** (R = aryl) that can be prepared in situ by mixing tartaric acid derivative and arylboronic acid at room temperature. In contrast to borane **3a**, which is both air- and moisture-sensitive, complex **3** (R = aryl or alkyl), is stable and can be stored in closed containers at room temperature (Equation 34). Catalyst **3** is effective in promoting the hetero-Diels–Alder reaction of aldehydes with Danishefsky's dienes to produce dihydropyrone derivatives of high optical purity (up to 98% ee) (Equation 35) [32]. The extent of asymmetric induction depends largely on the structure of the boronic acid. In general, bulky phenylboronic acids (R = 2,4,6-$Me_3C_6H_2$, *o*-$MeOC_6H_4$) result in excellent asymmetric induction. Judging from the product configuration, **3** should effectively cover the *si* face of the carbonyl when coordinated, and the selective approach of nucleophiles from the *re* face should agree well with the results of other **3**-catalyzed asymmetric reactions.

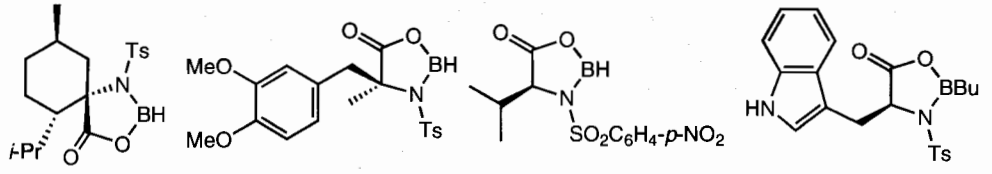




10.4.3
Enantioselective Mukaiyama Aldol Reactions

Following reports of the enantioselective aldol reaction using OXB under stoichiometric conditions by Kiyooka et al. in 1991 [33], Masamune et al. [34], Kiyooka et al. [35a], and Corey et al. [36] all independently developed OXB-catalyzed systems for enantioselective aldol reactions (Equation 36).





23 Masamune et al. (for X=OR[4] or SR[4])

24

25 Kiyooka et al. (for X=OR[4] or SR[4])

5b Corey et al. (for X=R[4])

According to Masamune et al., enantioselectivity is improved dramatically when complexes prepared from α,α-disubstituted glycine arylsulfonamides are used (eg. **23**, **24**). They suggested that the initial aldol adduct must undergo ring closure, as indicated by the arrows in Figure 10.9, to release **27** and to regenerate OXB [34]. In many cases, slow addition of the aldehyde to the reaction mixture has been beneficial

(permitting enough time for **26** to undergo ring closure) in improving the enantioselectivity of the reaction. Kiyooka et al. have reported a straightforward improvement of this reaction to a catalytic version by using a *N*-*p*-nitrobenzenesulfonyl-derived ligand and nitroethane instead of dichloromethane as solvent [35a].

An AM1 optimized structure of the chiral borane complex has been used by Kiyooka et al. to account for the stereochemical outcome of the reaction (Figure 10.9) [35a]. The aldehyde is suggested to coordinate to the boron on the face opposite the isopropyl substituent, thereby minimizing steric interactions. The Kiyooka model places the formyl-H over the five-membered ring chelate subtending an obtuse H–B–O–C dihedral angle. The preference for this orientation may result from the presence of a stabilizing anomeric interaction [35a]. Alternatively, the bound aldehyde may be locked in the conformation invoked by Kiyooka as a result of a formyl C–H hydrogen bond to the acyloxy donor, following the bonding model proposed by Corey [35a, 37].

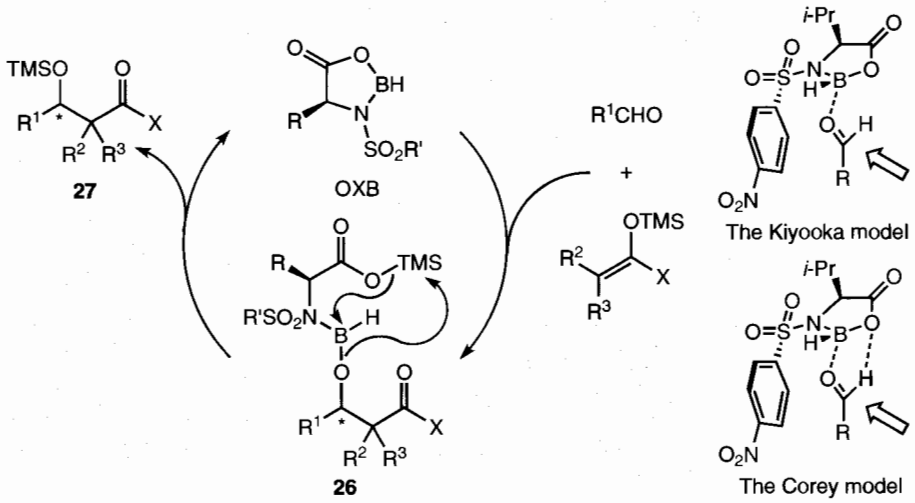
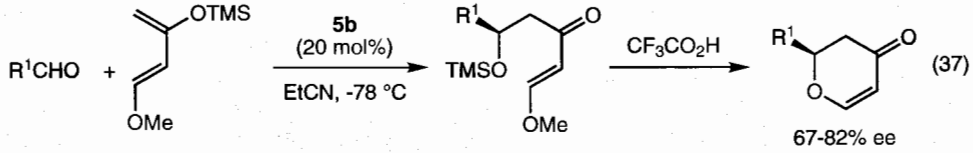


Figure 10.9 Proposed catalytic cycle and transition-state models.

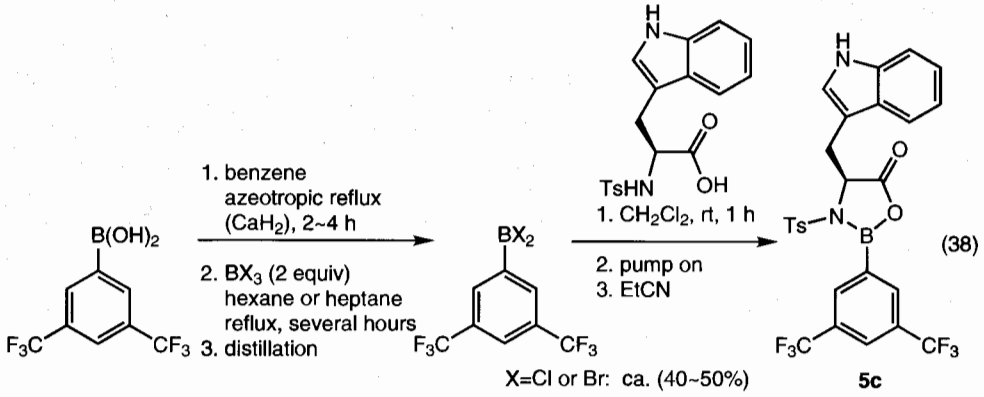
Corey et al. have used **5b** in the conversion of aldehydes into 2-substituted 2,3-dihydro-4*H*-pyran-4-ones by reacting them with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Equation 37) [36].

OXB **5** is highly effective for not only the Mukaiyama aldol reaction of aldehydes with silyl enol ethers [36] but also the Diels–Alder reaction of α-substituted α,β-enals with dienes [19]. However, more than 20 mol% of **5** is required for the former reac-



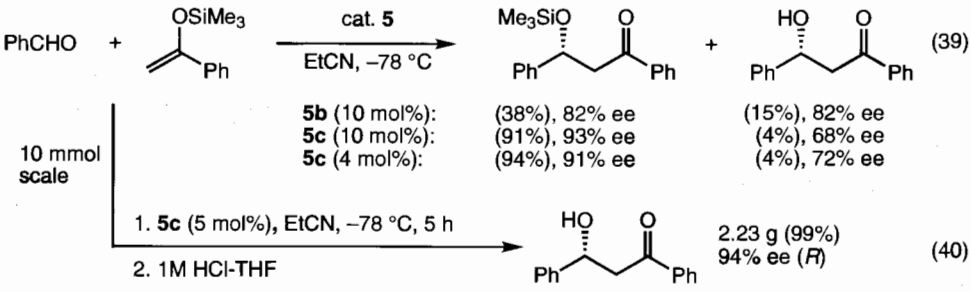
(37)

tion. Although other chiral oxazaborolidinones have been developed for the enantioselective aldol reaction of aldehydes with relatively more reactive ketene silyl acetals, they also require large amounts (more than 20 mol%) to give aldol adducts in good yield [34, 35]. Ishihara and Yamamoto et al. have developed the new, extremely active CAB catalyst **5c** using arylboron dichlorides bearing electron-withdrawing substituents as Lewis acid components [38]. Catalyst **5c** is prepared from *N*-(*p*-toluenesulfonyl)-(*S*)-tryptophan and 3,5-$(CF_3)_2C_6H_3BCl_2$ (Equation 38). Moisture-sensitive 3,5-$(CF_3)_2C_6H_3BCl_2$ and 3,5-$(CF_3)_2C_6H_3BBr_2$ are synthesized by dehydration of 3,5-$(CF_3)_2C_6H_3B(OH)_2$ to its trimeric anhydride and subsequent halogenation with BCl_3 and BBr_3, respectively [38]. The preparation of oxazaborolidinones from arylboron dichlorides has been also reported by Reilly and Oh [39] and Harada et al. [40]. Although **5b** has been prepared from *N*-(*p*-toluenesulfonyl)-(*S*)-tryptophan and butylboronic acid by dehydration [36], *B*-aryloxazaborolidinones can not be prepared from arylboronic acid, as observed by Nevalainen et al. [41] and Harada et al. [40b]. In contrast, **3**, R = aryl, can be easily prepared from 2,6-di(isopropoxy)benzoyltartaric acid and arylboronic acids at room temperature [42c].



According to Ishihara and Yamamoto et al. [38], benzaldehyde reacts with the trimethylsilyl enol ether derived from acetophenone in the presence of 10 mol% of **5b** to give the trimethylsilyl ether accompanied by the free aldol in respective yields of only 38% and 15% (Equation 39). However, when **5c** is used, catalytic activity and enantioselectivity are increased to a turnover of 25 and 91–93% ee, respectively. The absolute configuration of the aldol adducts is uniformly *R*. These results demonstrate that the introduction of an electron-withdrawing substituent such as 3,5-$(CF_3)_2C_6H_3$ group to the *B* atom of OXB is an effective method for enhancing their catalytic activity. The present method is especially attractive for large-scale synthesis (Equation 40).

OXB **5c** is effective for the reaction with not only terminal trimethylsilyloxy olefins but also trisubstituted (*E*)- and (*Z*)-trimethylsilyl enol ethers. The syn preference and the absolute preference for carbonyl *re*-face attack observed in the reactions of aldehydes with (*E*)- and (*Z*)-trimethylsilyl enol ethers suggests that the reaction occurs via an extended-transition state assembly (Figure 10.10) [36, 41]. Anti preference has



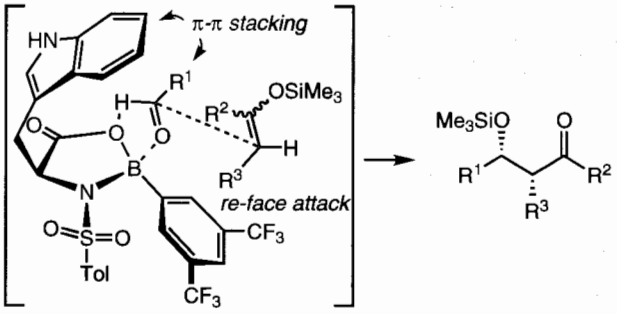
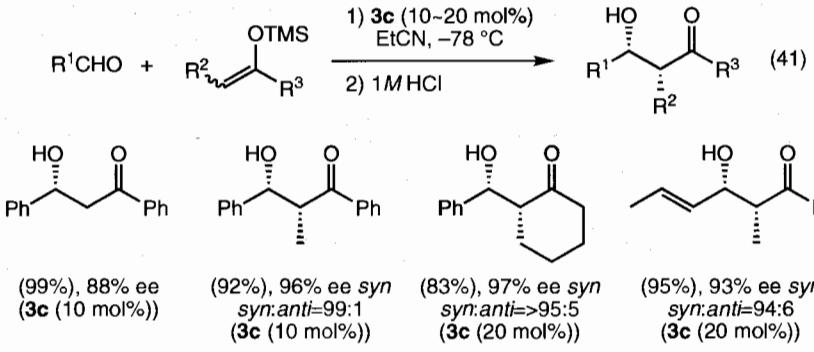


Figure 10.10 Proposed extended-transition state assembly.

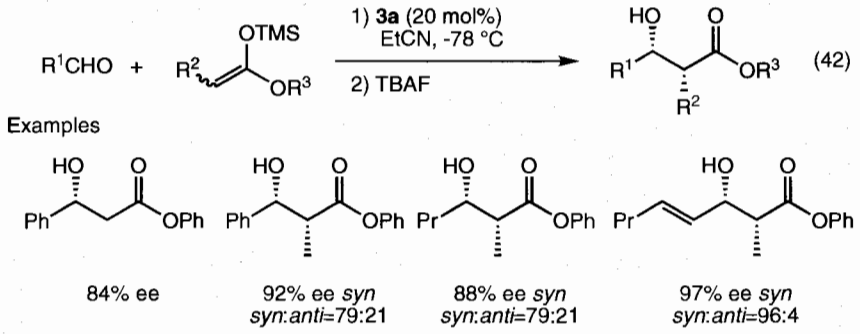
been observed in the reaction of aldehydes with (*E*)-ketene trimethylsilyl acetals catalyzed by other OXB [34, 35].

CAB **3a** is also an excellent catalyst (20 mol%) for the Mukaiyama condensation of simple enol silyl ethers of achiral ketones with various aldehydes. Furthermore, the reactivity of aldol-type reactions can be improved without reducing the enantioselectivity by using 10–20 mol% of **3c**. Enantioselectivity can also be improved without reducing the chemical yield by using 20 mol% of **3b**. The **3**-catalyzed aldol process allows for the formation of adducts in a highly diastereo- and enantioselective manner (up to 99% ee) under mild reaction conditions [41a, c]. These reactions are catalytic, and the chiral source is recoverable and reusable (Equation 41). The observed high syn selectivities, together with their lack of dependence on the stereoselectivity of the silyl enol ethers, in **3**-catalyzed reactions are fully consistent with Noyori's TMSOTf-catalyzed aldol reactions of acetals, and thus may reflect the acyclic extended transition state mechanism postulated in the latter reactions.

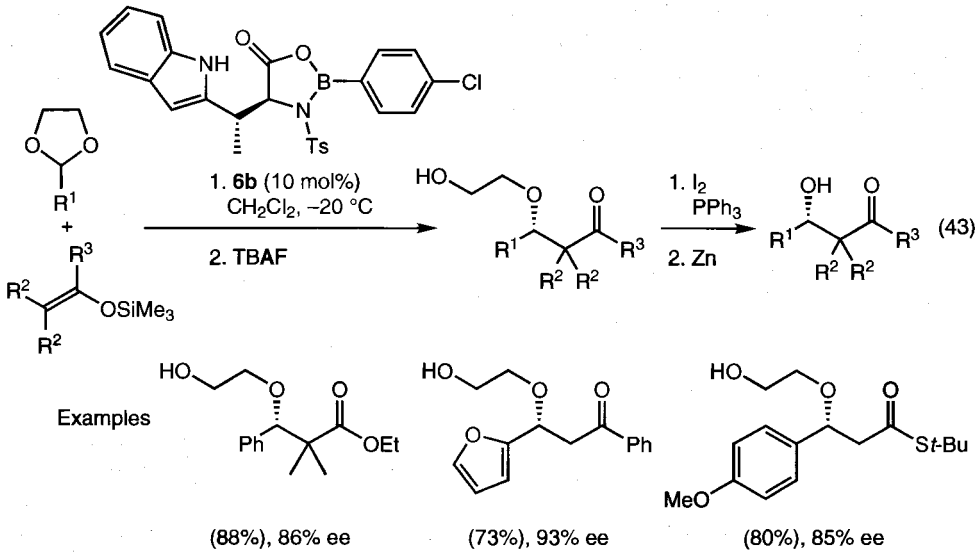
A catalytic enantioselective aldol-type reaction of ketene silyl acetals with achiral aldehydes also proceeds smoothly with **3a**, which can furnish erythro β-hydroxy esters with high optical purities (Equation 42) [42b, c]. A remarkable finding is the sensitivity of this reaction to the substituents of the starting silyl ketene acetals. The reactions of silyl ketene acetals derived from more common ethyl esters are totally stereorandom, and give a mixture of syn and anti isomers in even ratios with improved chemical yields. In sharp contrast, the use of silyl ketene acetals generated from phenyl esters leads to good diastereo- and enantioselectivities with excellent



chemical yields. The reason for this finding is not clear, but certain secondary interactions between electron-rich silyl ketene acetals derived from alkyl esters and Lewis acid may be responsible. Analogous to the previous results with enol silyl ethers of ketones, non-substituted silyl ketene acetals exhibit lower levels of stereoselectivity. Conversely, propionate-derived silyl ketene acetals show a high level of asymmetric induction. The reactions with aliphatic aldehydes, however, result in a slight reduction in optical yields. With phenyl ester-derived silyl ketene acetals, syn adducts predominate, but in most cases the selectivities are moderate compared to the reactions of ketone silyl enol ethers. Exceptions are α,β-unsaturated aldehydes, which show excellent diastereo-and enantioselectivities. The observed syn selectivities and *re*-face attack of nucleophiles on the carbonyl carbon of aldehydes are consistent with the aforementioned aldol reactions of ketone enol silyl ethers [42].

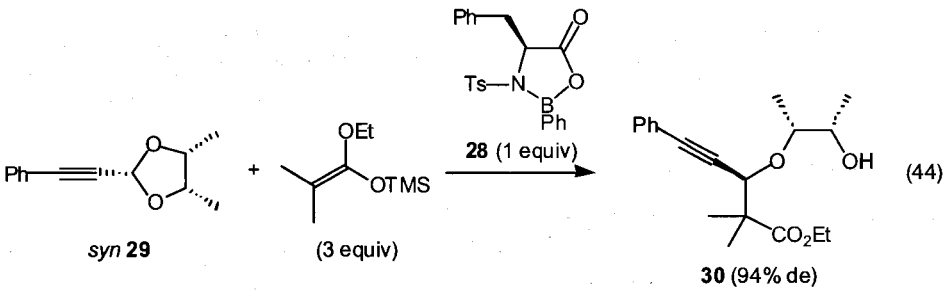


Harada et al. have reported that **6b** serves as an excellent catalyst for enantioselective ring-cleavage reactions of 2-substituted 1,3-dioxolanes with enol silyl ethers [40c]. Interestingly, **6** prepared from sulfonamide ligands and BH_3·THF does not exhibit appreciable catalytic activity [40a, b]. Successful results have been obtained in the ring cleavage of 1,3-dioxolanes with aryl and alkenyl groups at the 2-position. 2-Alkyl derivatives, however, react very sluggishly under these conditions. The 2-hydroxyethyl group in the ring-cleavage products can be removed simply by conversion into the iodides followed by treatment with zinc powder (Equation 43).



(43)

Desymmetrization of *meso*-1,2-diols has been realized by a chiral Lewis acid **28**-mediated enantioselective ring-cleavage of dioxolane derivatives [38d]. Treatment of *syn*-**29** with $Me_2C{=}C(OTMS)OEt$ and **28** at –78 °C gives the ring-cleavage product **30** (>20:1 diastereoselectivity) in 72% yield with 94% de (Equation 44); *anti*-**29** is unreactive under these conditions.

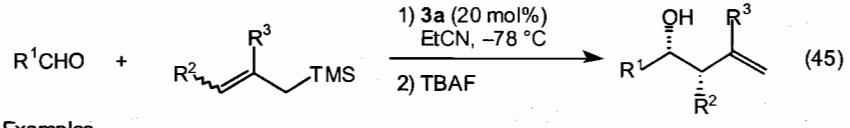


(44)

10.4.4
Enantioselective Sakurai–Hosomi Allylation Reactions

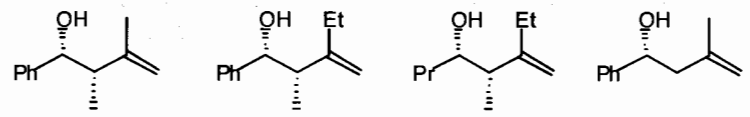
Asymmetric allylation is a valuable method for constructing chiral functionalized structures, and therefore many chiral allylmetal reagents directed toward a high level of asymmetric induction have been designed and synthesized. Although some of them have exhibited good to excellent enantio- and diastereoselectivities in reactions with achiral aldehydes, Yamamoto et al. developed the first method for a catalytic process in 1991 [43a]. CAB **3a** has a powerful activity in the Sakurai–Hosomi allyla-

tion reaction of aldehydes with allylsilanes and gives homoallylic alcohols in excellent enantiomeric excess (Equation 45). β-Alkyl substitution (R^2) at the olefin moiety of allylsilanes increases the reactivity, permitting a lower reaction temperature with improved asymmetric induction. γ-Alkylated allylsilanes exhibit excellent diastereo- and enantioselectivities to give syn homoallylic alcohols of higher optical purity. Regardless of the geometry of the starting allylsilanes, the predominant isomer in this reaction has syn configuration. The observed preference for the relative and absolute configurations of the homoallylic alcohols is predicted on the basis of an extended transition-state model similar to that for 3a-catalyzed aldol reactions [42].



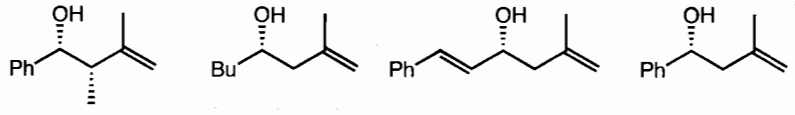
(45)

Examples



(64%), 92% ee *syn* 96% *syn* (81%), 96% ee *syn* 97% *syn* (36%), 86% ee *syn* 95% *syn* (68%), 82% ee

The boron substituent of **3c** strongly affects the chemical yield and the enantiomeric excess of the allylation adduct; 3,5-$(CF_3)_2C_6H_3B(OH)_2$ gives the greatest reactivity (Figure 10.11) [43b].

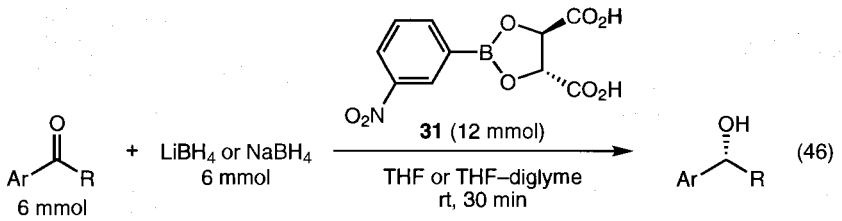


(82%), 91% ee *syn* *syn*:*anti* = 94:6 (70%), 63% ee (96%), 84% ee (99%), 88% ee

Figure 10.11 Examples of allylation catalyzed by **3c** (10–20 mol%).

10.4.5
Enantioselective Reduction

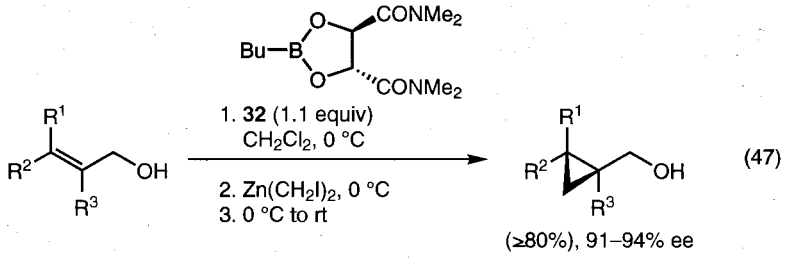
High enantioselectivities are obtained using tartaric acid-derived boronate ester **31** in combination with lithium borohydride or sodium borohydride for asymmetric reduction of alkyl or aryl ketones. The chiral Lewis acid is easily prepared in one hour, and the resulting alcohols are obtained in enantiomeric excesses of 88–99% (Equation 46) [44].



(46)

10.4.6
Enantioselective Cyclopropanation

High enantioselectivities are obtained using *N,N,N′,N′*-tetramethyltartaric acid diamide-derived boronate ester **32** in combination with bis(iodomethyl)zinc for asymmetric cyclopropanation of allylic alcohols. Various chiral, non-racemic cyclopropylmethanols can be obtained in enantiomeric excesses of 91–94%. This methodology has been extended with success to the cyclopropanation of unconjugated and conjugated polyenes and homoallylic alcohols (Equation 47) [45].



(47)

10.5
Conclusions

Diarylborinic acids and arylboronic acids bearing electron-withdrawing substituents are useful as air-stable Lewis acid catalysts for various organic transformations. In particular, the potential of 3,5-$(CF_3)_2C_6H_3B(OH)_2$ as a Lewis acid catalyst has strikingly increased since Yamamoto and Ishihara's initial study [32b]. Continued exploratory research on the application of arylboron compounds as air-stable and reusable catalysts is expected to provide powerful and practical methods for various Brønsted–Lewis acid-catalyzed organic transformations.

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11
Oxazaborolidines as Asymmetric Inducers for the Reduction of Ketones and Ketimines

Byung Tae Cho

11.1
Introduction

Optically active alcohols and amines are important compounds utilized extensively as starting materials, intermediates, and chiral auxiliaries for preparing biologically active substances, including natural products. One of the simplest and most useful methods for the preparation of such compounds is the asymmetric reduction of prochiral ketones and ketimines. Recently, significant advances have been made in enantioselective ketone reduction using stoichiometric and catalytic boron-based reagents [1–3]. Despite much remarkable success, however, limitations to the use of stoichiometric reagents are availability, cost, ease of product purification and chiral auxiliary recovery on large-scale applications, as at least one equivalent of the reagents is required for the reduction. Thus it appeared desirable to develop catalytic processes for the reduction. The discovery of oxazaborolidine (OAB)-catalyzed reductions by Itsuno's [4] and Corey's [5] groups provides an impetus for asymmetric reduction, because the transformation furnishes high enantioselectivity with predictable configurations even in the presence of only 2 mol% of OAB.

In contrast to the enormous progress in the asymmetric reduction of ketones, the reduction of ketimines with chiral reducing agents has been relatively neglected. Few successful asymmetric reductions to the corresponding amines with high enantioselectivity have been reported [6a]. Although several applications of the OAB-induced asymmetric reduction methodology to the synthesis of non-racemic natural products and intermediates has been reported, this chapter is not designed to be completely comprehensive, but rather to summarize recent advances in such reductions of various prochiral ketones and ketimines (Figures 11.1 and 11.2, respectively), and will cover results reported until 2003. Prior to this chapter, excellent reviews for the asymmetric reductions using boron-based reducing agents have been published [1–3, 6].

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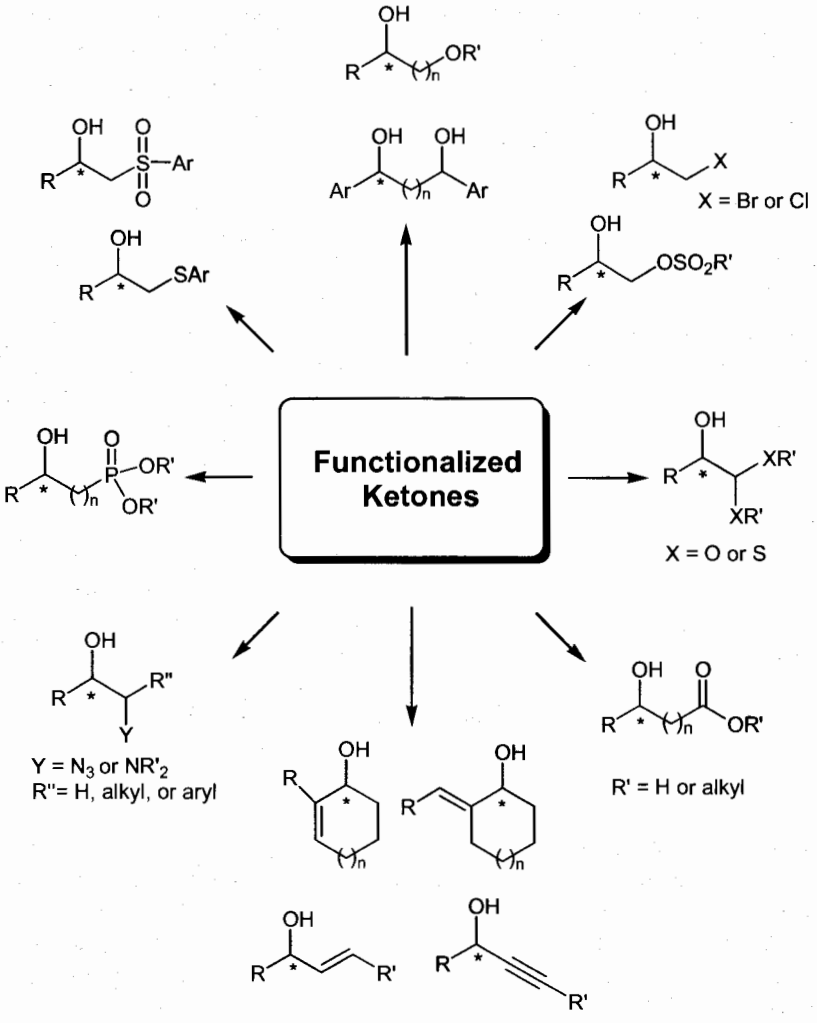
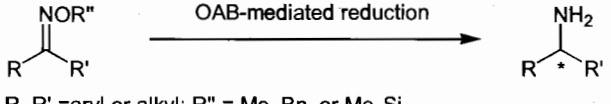


Figure 11.1 OAB-catalyzed asymmetric reduction of functionalized ketones.



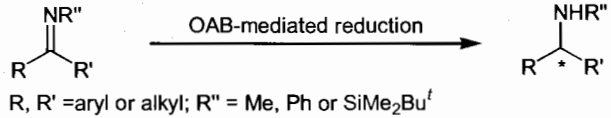
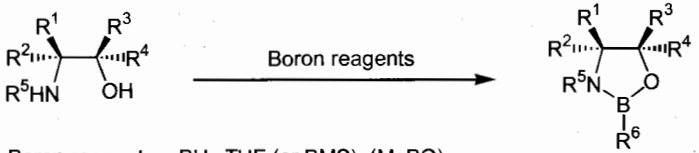


Figure 11.2 OAB-induced asymmetric reduction of ketimine derivatives.

11.2 Oxazaborolidines

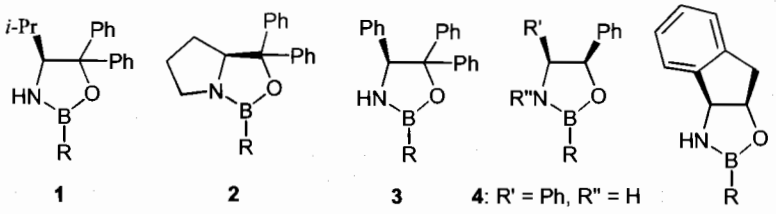
Since the structure of 1,3,2-oxazaborolidine (OAB) derivatives was first characterized by Corey, Bakshi, and Shibata [5], several oxazaborolidines and their applications as catalysts for asymmetric reduction of prochiral ketones have been reported [1, 3, 7–22]. Most of them were prepared from chiral 1,2-amino alcohols and borane, substituted boronic acids, trimethylboroxine or trimethylborate (Scheme 11.1). Amino alcohols used include naturally occurring chiral 1,2-amino alcohols, such as ephedrine and norephedrine, amino alcohols derived from chiral pools, including α-amino acids, D-camphor and D-mannitol, and other synthetic chiral amino alcohols. Generally, *B*-alkyl OABs are more stable in air and moisture than *B*-H analogues. Of the reagents reported, OABs **1**–**7** [4, 5, 23–26] (Figure 11.3) have been applied widely to the asymmetric reduction of functionalized ketones and ketimines. During the past ten years, efficient methods for the reduction using polymer- or nickel boride-bound chiral OABs as catalyst have been successfully developed [27–34]. Industrially, these procedures provide very attractive features because of the easy of recovery of catalysts and simple separation of products from the reaction mixture and applicability as a useful tool for automated reactions.



Boron reagents = BH_3-THF (or BMS), $(MeBO)_3$, *n*-BuB(OH)$_2$, PhB(OH)$_2$ or B(OMe)$_3$

R^1,R^2,R^3,R^4 = H, alkyl or aryl; R^5 = H or alkyl; R^6 = H, Me, *n*-Bu, Ph or OMe

Scheme 11.1 Preparation of oxazaborolidines (OAB).



1 **2** **3** **4**: R' = Ph, R" = H **7**

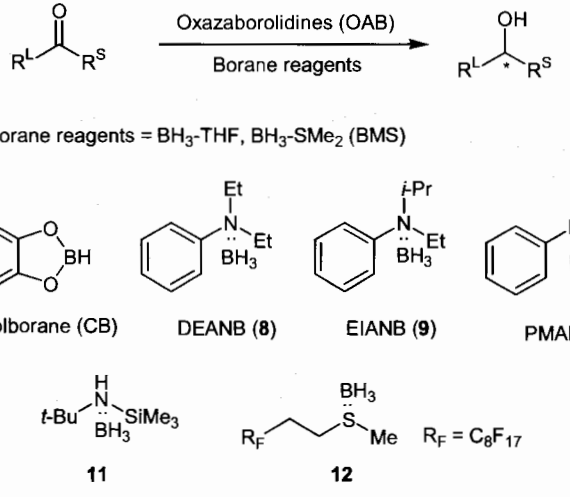
a, R = H; **b**, R = Me; **c**, R = *n*-Bu; **5**: R' = R" = Me

d, R = Ph; **e**, R = OMe; **f**, R = CH_2TMS **6**: R' = Me, R" = H

Figure 11.3 Selected chiral oxazaborolidines.

11.3
Oxazaborolidine-catalyzed Asymmetric Reduction of Ketones

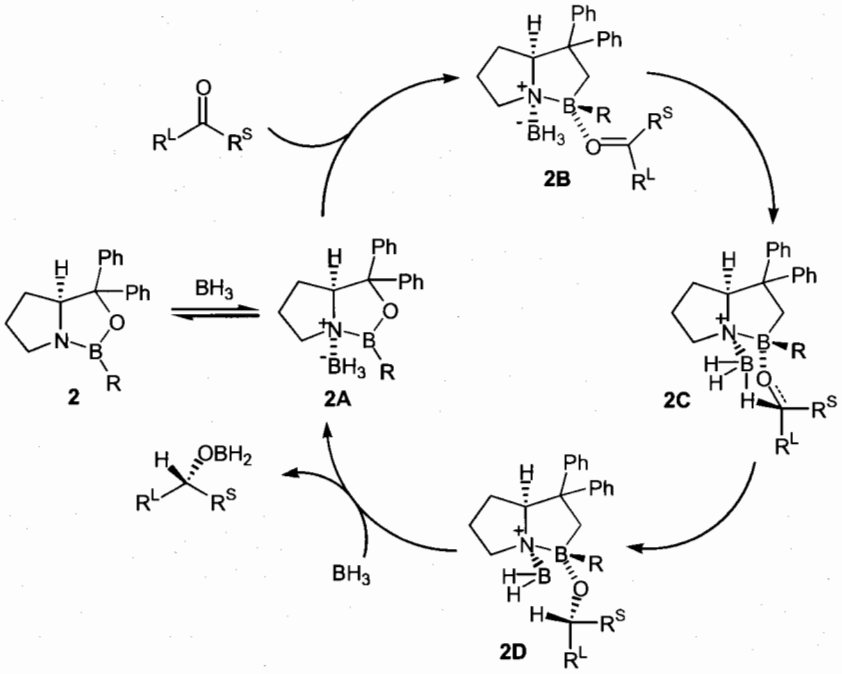
The general procedure for OAB-catalyzed borane reduction of prochiral ketones to give high enantioselectivity is as follows: 1.0 equiv. of a prochiral ketone dissolved in solvent is added slowly, over 1–3 h at ambient temperature, to a mixture of 2–10 mol% of OABs and 1.5–3.0 equiv. (as hydride) of borane reagent in an appropriate solvent. Reduction of ketones is usually complete within 10 min. THF and toluene were used as preferable solvent. In this procedure, borane-THF (BH_3·THF), borane-dimethyl sulfide (BMS) and catecholborane (CB) are commonly utilized as the stoichiometric effective borane reagents. However, these borane reagents have certain disadvantages, such as the low concentration and stability of BH_3·THF, and high volatility, flammability, unpleasant odor of BMS and high sensitivity to air and moisture. Moreover, Matos and co-workers reported recently that a borohydride species added to commercial BH_3·THF as a stabilizer participates in nonselective ketone reduction or interacts with the catalyst to lower the enantioselectivity in the OAB-catalyzed borane reduction. In fact, the reduction of acetophenone with commercial 1M BH_3·THF (stabilized with ~0.005M $NaBH_4$, >98% purity) in the presence of 5 mol% of *ent*-**2b** in THF at ambient temperature gave 1-phenyl ethanol with 65% ee, while the same reduction using nonstabilized 1 M BH_3·THF provided 95% ee [35]. These drawbacks could be overcome by using amine-borane complexes, such as *N,N*-diethylaniline-borane (DEANB, **8**) [36], *N*-ethyl-*N*-isopropylaniline-borane (EIANB, **9**) [37], *N*-phenylmorpholine-borane (PMANB, **10**) [37] and *N-tert*-butyl-*N*-trimethylsilylamine-borane (**11**) [38], and odorless fluorous solid borane complex **12** [39] as borane reagents (Scheme 11.2). Such amine-borane complexes and fluorous borane complex not only afford excellent enantioselectivities in the reduction of acetophenone, but also offer the advantages of being soluble in most common solvents at high concentration and have a lower sensitivity to air and moisture.



Scheme 11.2 Various borane reagents used in OAB-catalyzed reduction.

11.3.1
Mechanism of OAB-catalyzed Ketone Reduction

Scheme 11.3 outlines the general mechanistic model developed for the **2**-catalyzed reduction of ketones [5a, 7c]. Reductions may occur by the following sequence: (a) complexation of borane to the nitrogen of **2**; (b) anti-coordination of the ketone oxygen to the ring boron of **2**; (c) hydrogen transfer from the coordinated borane to the carbonyl via a six-membered cyclic transition state. The initial step in the pathway is rapid coordination of BH_3 to the Lewis base nitrogen atom on the α face of **2** to form **2**·BH_3 adduct (**2A**), which has been structurally defined by single-crystal X-ray diffraction analysis [5c]. This adduct serves to activate BH_3 as a hydride donor and also to increase the Lewis acidity of the boron atom of the OAB ring, which coordinates with the carbonyl oxygen of the ketone to provide the more stable anti form along the direction of the oxygen lone pair. The manner of this coordination minimizes unfavorable steric interactions between **2** and the ketone to form the complex **2B**. The resulting complex produces reduction product **2D** by a face-selective hydride transfer via a six-membered transition state **2C**. Finally, catalyst **2** is regenerated by decomposition of **2D** with excess BH_3.

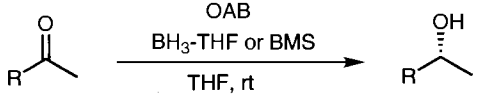


Scheme 11.3 Proposed mechanism of the **2**-catalyzed reduction of ketones.

11.3.2
Unfunctionalized Acyclic and Aryl Alkyl Ketones

In general, OAB-catalyzed reductions are mostly effective for prochiral ketones having significantly different steric bulk between the two groups adjacent to the carbonyl to give high enantioselectivities. For example, the reduction of aryl alkyl ketone and hindered aliphatic ketone such as acetophenone and pinacolone, respectively, provided high enantioselectivities, whereas that of unhindered aliphatic ketones, namely 2-hexanone and 2-octanone, provide low to moderate enantioselectivities (Table 11.1).

Table 11.1 Enantioselectivities in the reduction of simple ketones.



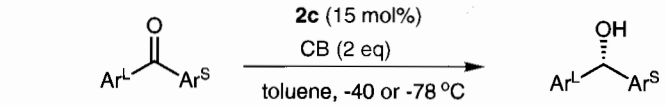
R = Ph, *t*-Bu, *n*-C_4H_9 or *n*-C_6H_{13}

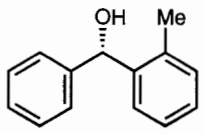
OAB	Mol%	PhCOMe	*t*-BuCOMe	RCOMe	Reference
1a	100	94	74	55 (R = *n*-C_4H_9)	4b
2b	10	96.5	97.3	61 (R = *n*-C_6H_{13})	5b,36
3a	10	96	92	70 (R = *n*-C_6H_{13})	22
4a	5	94	82	72 (R = *n*-C_4H_9)	23a
6a	5	84	78	68 (R = *n*-C_4H_9)	23a
7a	5	88	95	79 (R = *n*-C_6H_{13})	25b

11.3.3
Diaryl Ketones

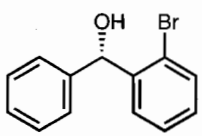
Prochiral diaryl ketones have been reduced, with 2 equiv. of CB in the presence of 0.15 equiv. of **2c** in toluene at −40 °C or −78 °C, to provide (*R*)-benzhydrols with 81–97% ee (Table 11.2) [40]. Interestingly, ortho-substituted aryl groups act as a smaller bulky group than a phenyl group. This has been explained by steric interaction between an ortho-substituent and the carbonyl oxygen, which causes the substituted aryl ring to be twisted out of the carbonyl plane and, thus, effectively to behave as a smaller substituent than an unsubstituted aromatic ring [40]. Reduction of *p*-methoxy-*p*′-nitrobenzophenone gave the corresponding (*R*)-benzhydrol with 81% ee, showing that a *p*-methoxyphenyl acts as a bulkier group than *p*-nitrophenyl as a result of gearing effects between the aromatic rings. For 1-bromofluorenone, stoichiometric reduction using **2a**-BH_3 provided the product alcohol with 84% ee in 13% yield [41].

Table 11.2 Reduction of diarylketones.

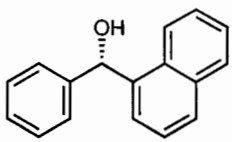




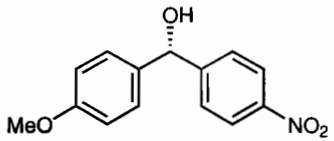
97% ee



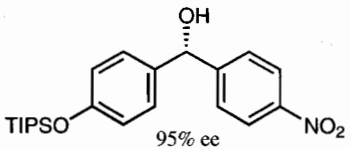
97% ee



97% ee



81% ee

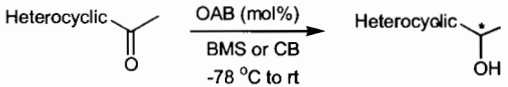


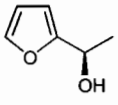
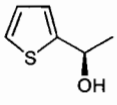
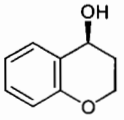
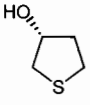
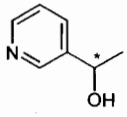
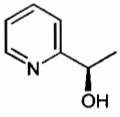
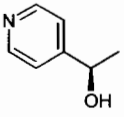
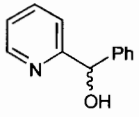
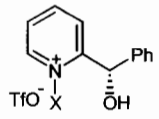
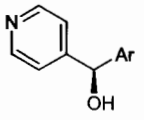
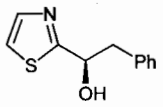
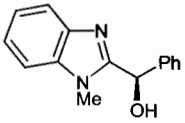
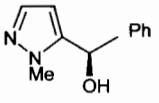
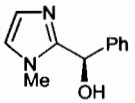
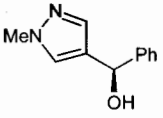
95% ee

11.3.4
Heterocyclic Ketones

As shown in Table 11.3, the reduction of heterocyclic ketones, such as 2-acetylfuran, 2-acetylthiophene and 4-chromnone using **2a** or *ent*-**2b** as catalyst provided excellent enantioselectivities (91–96% ee) [42, 43]. However, tetrahydrothiophen-3-one, with a similar steric size for the two groups attached to the carbonyl, gave a low enantioselectivity (23% ee). In most reductions of acyl pyridine derivatives, stoichiometric reduction provided better enantioselectivities [6b, 23, 24a, 43]. These results may be attributable to a non-enantioselective reduction that occurs through hydrogen transfer from the borane coordinated to the pyridine nitrogen. Interestingly, *B*-OMe-OAB catalyst, **2e** [44b], prepared in situ from (*S*)-diphenylprolinol and trimethylborate, which is more acidic than **2a** and **2b**, was more effective for such reduction [44a]. As expected, increasing the catalyst loading from 0.2 to 1.0 equiv for the reduction of 2-acetylpyridine using **2e** raised the enantioselectivity from 22% to 98%. Although the reduction of 2-benzoylpyridine by CB in the presence of 15 mol% of **2c** in toluene at −40 °C provided a racemic mixture of product alcohol in 89% yield, the reduction of its *N*-methyl or *N*-allyl pyridinium substrates afforded high enantioselectivities (>90% ee) [40a]. Similarly, the reduction of 2-(*p*-methoxybenzoyl)pyridine provided very high enantioselectivity by masking the pyridine lone pair by complexation with BF_3-etherate [40a]. Stoichiometric reduction of 2-thiazolyl benzyl ketone with **2d**-BH_3 took place with high enantioselectivity [44a]. OAB-catalyzed reduction of various pyrazole phenyl ketones afforded moderate enantioselectivities [45]. In these cases, the pyrazole rings behaved as the small groups.

Table 11.3 Reduction of heterocyclic ketones.

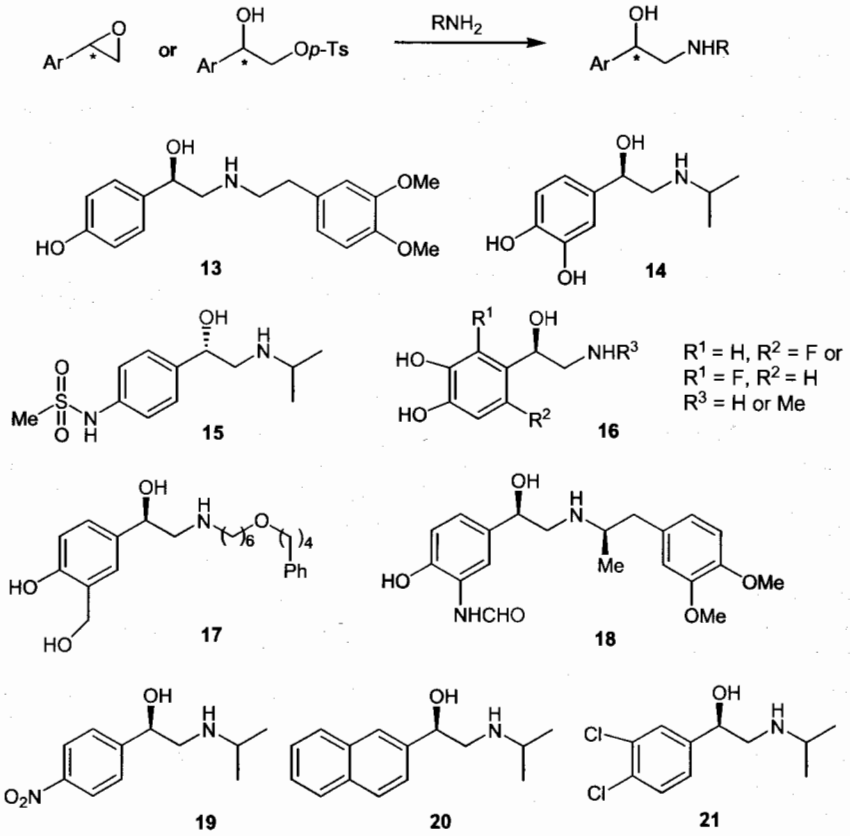


			
2a (20), 93% ee	**2a** (20), 91% ee	*ent*-**2b** (5), 96% ee	**2c** (5), 23% ee
			
1a (100) 73% ee, *R* *ent*-**2b** (5) 51% ee, *S* *ent*-**2b** (100) 80% ee, *S* **2e** (10) 99% ee, *R* **3b** (100) 95% ee, *R* **4a** (5) 96% ee, *R*	*ent*- **2b** (20) 45% ee **2e** (20) 22% ee **2e** (100) 98% ee	*ent*- **2b** (20), 65% ee **2e** (10), 99% ee	**2c** (15), CB (2 eq), -40 °C, *dl*
			
	2c (15), CB (2 eq), -40 °C: X=Me, >90% ee; X=allyl, 99% ee	Ar = H: **2e** (10), 83% ee; Ar = 4-MeOC$_6$H$_4$: **2c** (15), $BF_3 \cdot OEt_2$, CB (1.5 eq), -78 °C, 93% ee,	**2e** (100), 94% ee
			
ent-**2b** (15), CB (2 eq), -10 °C-rt, 23% ee	*ent*-**2b** (15), CB (2 eq), -15 °C-rt, 98% ee	*ent*-**2b** (15), CB (2 eq), -15 °C-rt, 8% ee	*ent*-**2b** (15), CB (2 eq), -10 °C-rt, 81% ee

11.3.5
Functionalized Ketones

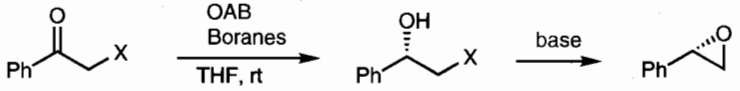
11.3.5.1 α-Halo and α-Sulfonyloxy Ketones

Optically active halohydrins or styrene oxide derivatives obtained by the reduction of α-halo ketones followed by treatment with base have been widely used as key intermediates in the synthesis of many chiral drugs containing the β-amino alcohol moiety. Examples of such drugs include (*R*)-denopamine (**13**) [46a], (*R*)-isoproterenol (**14**) [46b], *d*-solatol (**15**) [47], (*R*)-fluoro(nor)epinephrine (**16**) [48], (*R*)-salmeterol (**17**) [49], and (*R,R*)-formoterol (**18**) [50] (Scheme **11.4**). Most OABs were effective for the reduction of 2-bromo- or 2-chloroacetophenone derivatives (**22**), providing the corresponding halohydrins with high enantioselectivities (Table 11.4).



Scheme 11.4 Applications of chiral styrene oxides and 1,2-diol monotosylates to the synthesis of some chiral drugs.

Table 11.4 Reduction of α-halo- and α-*p*-tosyloxyacetophenone using various OABs.

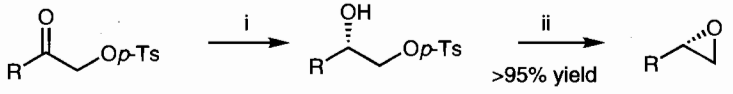


22: X = Cl or Br; **23**: X = *p*-TsO

OAB	Mol%	Boranes	22 (% ee)	23 (% ee)
1a	100	$BH_3 \cdot THF$	96	
1b	10	**9**		94
2b	10	$BH_3 \cdot THF$	95.3	
2b	10	**9**		99
3a	100	$BH_3 \cdot THF$	95	
4a	5	BMS	92	
4b	10	**9**		77
7b	10	$BH_3 \cdot THF$	96	
7b	10	**9**		78

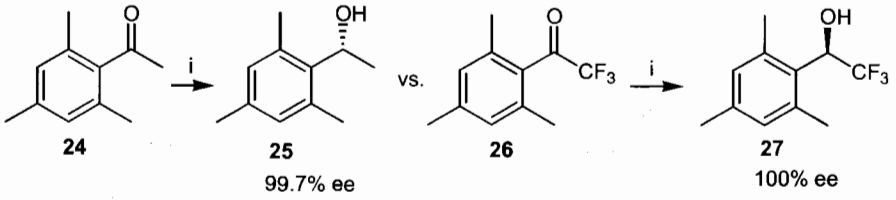
However, the use of α-halo ketones as starting materials in commercial applications has severe drawbacks: α-halo ketones cause skin and eye irritation and are unstable to light. These disadvantages were overcome by using the more stable and non-irritating α-sulfonyloxy ketones. Comparing the reductions of α-*p*-tosyloxyacetophenone (**23**) with **9** using various OAB catalysts, the **2b**-catalyzed reduction provided the best result to give the corresponding 1,2-diol monosulfonates and terminal epoxides in very high enantioselectivities (Table 11.5) [51]. The reduction was very effective for most aromatic analogues, giving excellent enantioselectivities. However, 1-(2-chlorophenyl)-2-(*p*-tosyloxy)ethanone was reduced with a relatively low enantioselectivity (80% ee), owing to the above-mentioned ortho-substituent effect on phenyl ring. Using this methodology, chiral drugs such as (*R*)-nifenalol (**19**), (*R*)-pronethalol (**20**) and (*R*)-dichloroisoproterenol (**21**) were successfully prepared (Scheme 11.4) [52]. For aliphatic analogues, the bulky 1-cyclohexyl-2-(*p*-tosyloxy)ethanone was reduced with a high enantioselectivity. Unlike CH_2X groups in the OAB-catalyzed reduction of α-halo ketones, CX_3 (X = halogen) groups behave as the bulkier group even against alkyl or aryl groups such as *tert*-Bu, mesityl, anthryl and 1-adamantyl. These results have been attributed to electronic factors of the CX_3 group [53c]. For example, the reduction of acetylmesitylene (**24**) with CB in the presence of 10 mol% of **2c** in toluene at –78 °C afforded (*R*)-1-mesitylethanol (**25**) with 99.7% ee, while trifluoroacetylmesitylene (**26**) reduced under identical conditions provided (*R*)-mesityl-2,2,2-trifluoroethanol (**27**) with 100% ee (Scheme 11.5) [53a]. In the reduction of $PhCOCX_3$, the increasing steric size of CX_3 led to an increase in selectivity, such as 90% ee at –78 °C for $PhCOCF_3$, 96% ee at –23 °C for $PhCOCCl_3$ and 98% ee at –23 °C for $PhCOCBr_3$ [52b–d]. Similarly, the reduction of (trifluoroacetyl)biphenyl derivatives provided high enantioselectivity [8].

Table 11.5 Reduction of α-*p*-tosyloxyketones.



i. **2b** (10 mol%), **9** (1.0 eq), THF, 25 °C
ii. aq. 2M NaOH, ether

Epoxides							
R	**% ee**	**R**	**% ee**	**R**	**% ee**	**R**	**% ee**
Ph	99	4-ClC_6H_4	99	4-MeC_6H_4	97	2-Naph	100
2-ClC_6H_4	80	3,4-$Cl_2C_6H_3$	94	4-$NO_2C_6H_4$	97	*n*-C_7H_{15}	40
3-ClC_6H_4	99	4-FC_6H_4	98	4-PhC_6H_4	98	*c*-C_6H_{11}	96



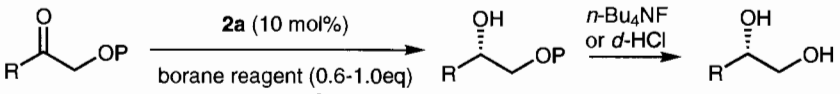
i. **2c** (10 mol%), CB (1.5 eq), toluene, -78 °C

Scheme 11.5 Electronic effect of CF_3 group in the **2c**-catalyzed ketone reduction.

11.3.5.2 α-Hydroxy Ketones and Diketones

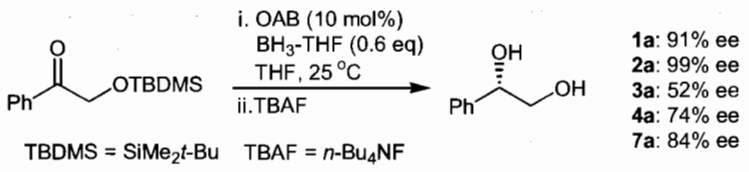
Recently, efficient and very highly enantioselective methods for the preparation of optically active terminal 1,2-diols via the OAB-catalyzed borane reduction of α-silyloxy or tetrahydropyranyloxy ketones have been reported (Table 11.6) [54a,b]. Of the various OABs examined for the reduction of 2-*tert*-butyldimethylsilyloxyacetophenone, **2a** provided the best result to give 1-phenyl-1,2-ethanediol with near 100% ee (Scheme 11.6). Conversely, **2a**-catalyzed reductions of 1,2-diketones (in particular, benzil derivatives and heterocyclic analogs) provided optically active (*S,S*)-hydrobenzoins with both high enantiomeric and diastereomeric selectivity (Scheme 11.7) [55]. Similar reductions of aliphatic and aromatic 1,4-, 1,5- or 1,6-diketones produced the corresponding diols with moderate to high enantiomeric and diastereomeric selectivity [56].

Table 11.6 Reduction of α-protected hydroxy ketones.

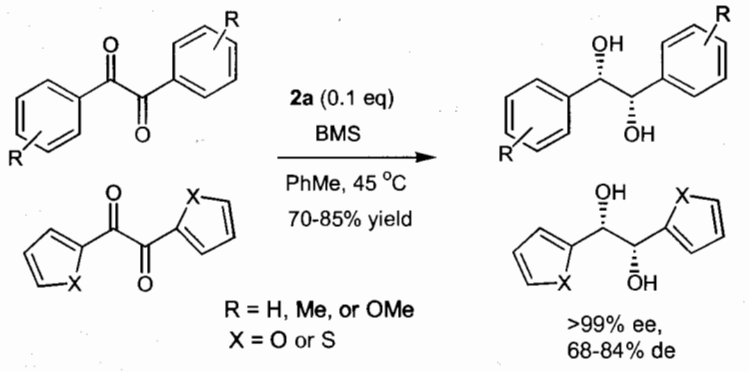


P = $SiMe_2$*t*-Bu (TBDMS), Si(*i*-Pr)$_3$ (TIPS), or 2-tetrahydropyranyl (THP)
borane carrier = BH_3-THF, **8** or **9**

				Diols			
R	**% ee**	**R**	**% ee**	**R**	**% ee**	**R**	**% ee**
Ph	99	4-ClC_6H_4	95	Et	73–88	*c*-C_6H_{11}	96–97
4-MeC_6H_4	99	4-$MeOC_6H_4$	99	*i*-Pr	75–91		
4-BrC_6H_4	99	2-Naph	99	*t*-Bu	97		



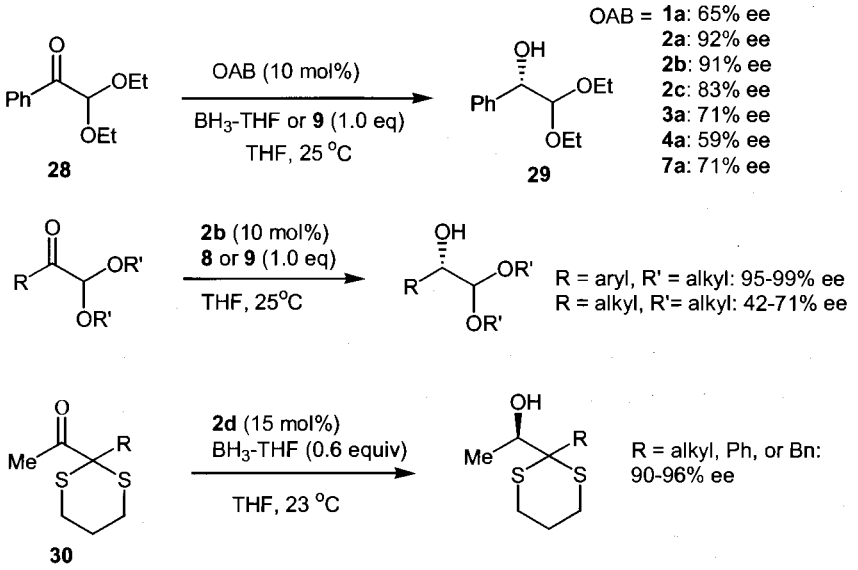
Scheme 11.6 OAB-catalyzed reduction of α-silyloxy ketones.



Scheme 11.7 **2a**-catalyzed reduction of 1,2-diketones.

11.3.5.3 α-Keto Acetals and Thioketals

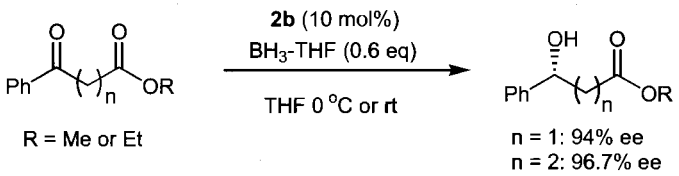
From a comparison study of asymmetric reduction of a selected α-keto acetal, 2,2-diethoxy-1-phenylethanone (**28**), using various OAB catalysts, the use of **2a** or **2b** and **8** or **9** as catalyst and borane reagent, respectively, provided the best result to give product α-hydroxy acetal **29** in 96–99% yield and >90% ee (Scheme 11.8) [57]. Such reduction was highly effective for aromatic ketones but less so for aliphatic ones. The **2d**-catalyzed reductions were highly enantioselective for both aliphatic and aromatic α-keto thioketals **30** [58].



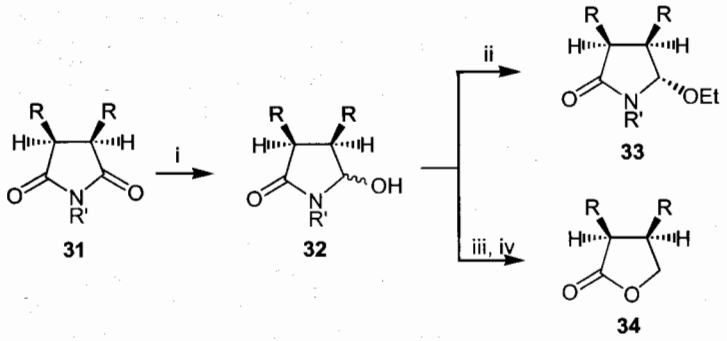
Scheme 11.8 OAB-catalyzed reduction of α-keto acetals and thioketals.

11.3.5.4 Keto Esters and *meso*-Imides

The **2b**-catalyzed reduction of γ or δ-keto esters provided the corresponding hydroxy esters with high enantioselectivity (Scheme 11.9) [5b], while the reduction of α-keto esters was less effective [6b, 44b, 59]. Desymmetrization of *meso*-imides **31** via stereoselective reduction is one of the most powerful transformations to provide products with three new chiral centers. Such transformations with good enantioselectivities were achieved by OABs-catalyzed reductions (Scheme 11.10) [60–62]. The hydroxy lactams **32** obtained were easily converted into ethoxy lactams **33** by acidic ethanolysis, and were transformed into chiral lactones **34** by sodium borohydride reduction.

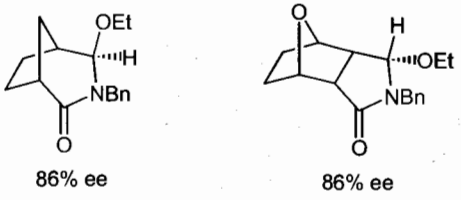


Scheme 11.9 **2a**-catalyzed reduction of keto esters.



i. **2a** (10-50 mol%), BH_3-THF (0.6-0.75 eq), 0 °C-rt, 47-95% yield. ii. H^+, EtOH, 53-100% yield. iii. $NaBH_4$, EtOH, 60 °C. iv. 2 M H_2SO_4, 80 °C, 59-95% yield from **32**

33					
R	R'	% ee	R	R'	% ee
OAc	Bn	87	-$(CH_2)_4$-	Bn	80
-CH_2-	Bn	88	-$(CH_2)_4$-	Ph	68
-$(CH_2)_2$-	Bn	89	-$(CH_2)_4$-	*c*-C_6H_{11}	94
-$(CH_2)_3$-	Bn	77	-$(CH_2)_4$-	$(CH_2)_2CN$	90



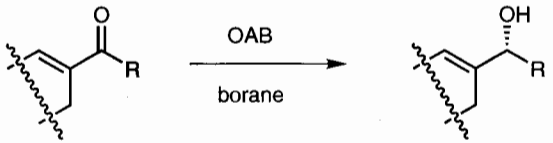
Scheme 11.10 Desymmetrization of meso-imides via **2a**-catalyzed reduction.

11.3.5.5 α,β-Enones and Ynones

Reduction is effective for all cases having acyclic [40b, 63–65], endocyclic [5b, 53b, 63, 66], or exocyclic double bonds (Table 11.7) [67]. To minimize hydroboration of the C=C bond by borane, reductions using CB as hydride source were mainly carried out at low temperatures. Interestingly, the olefinic portion in α,β-enones generally behaves as the large group for the reduction. Enantioselective reduction of α,β-acetylenic ketones is also very important because the chiral propargylic alcohol products can be transformed into many other functional groups. Table 11.8 summarizes highly effective OAB-mediated reductions of α,β-ynones with stoichiometric and catalytic methods. Reductions using stoichiometric amounts or excess of **2b** [68] and *ent*-**3b** [69] provided the corresponding propargylic alcohols with good to high enantioselectivities, showing that the enantioselectivities are generally more sensitive to the steric size of the substituents on the carbonyl carbon than that of the distal group of the alkyne. In these reductions, the alkynyl moiety behaves as the smaller group, and

catalytic effects of OABs used are also effective. The enantioselectivity of the OAB reduction also depends on the steric size of the boron substituent in the catalysts (Scheme 11.11). These results are due to a remote steric effect across the C–C triple bond involving the distal *i*-Pr_3Si substituent of the substrate and the Me_3SiCH_2 group on the boron atom of catalyst **2f** [70].

Table 11.7 Reduction of α,β-enones.



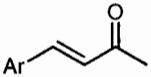
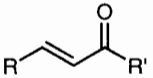
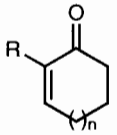
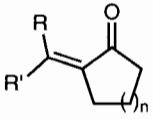
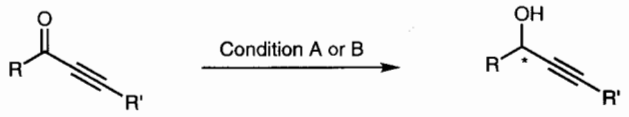
	Ar =	OAB (mol%)	Boranes (eq)	°C (solvent)	Yield (%)	% ee
	Ph	**2c** (15)	CB (1.1)	–78 (toluene)	90	97
	Ph	*ent*-**10** (10)	BMS (1.0)	0 (THF)	>90	82
	4-MeOPh	**2c** (15)	CB (1.1)	–78 (toluene)	88	95
	4-NO_2Ph	**2c** (15)	CB (1.1)	–78 (toluene)	88	72
	R, R' = alkyl	*ent*-**3a** (10)	BMS (1.0)	0 (THF)	>90	63–91
	R = Alkyl or Br n = 0 or 1	**2b** or **2c** (10)	CB (1.5), BMS (1.0) or BH_3·THF(0.6)	–78 to 23 (toluene or THF)	>90	81–97.5
	R = H or alkyl R'= alkyl or Ph n = 0 or 1	**2b** (100)	BMS (1.0)	–20 (CH_2Cl_2)	50–98	87–>95

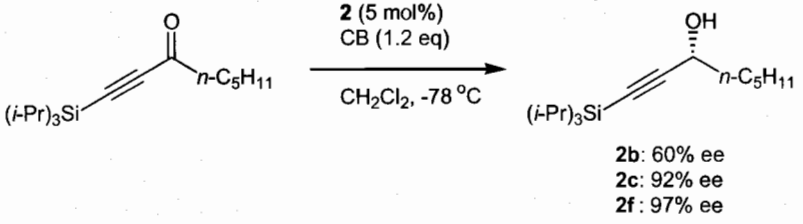
Table 11.8 Reduction of α,β-ynones.



Condition A: **2b** (200 mol%), BMS (5 eq), THF, -30 °C
Condition B: *ent*-**3b** (100 mol%), BMS (1.2 eq), THF, 0 °C

R	R'	Yield (%)	% ee	R	R'	Yield (%)	% ee
n-C_7H_{15}	H	54	95, *S*	$PhCH_2CH_2$	H	73	90, *R*
c-C_6H_{11}	H	81	98, *S*	$PhCH_2CH_2$	H	65[a]	80[a], *R*
c-C_6H_{11}	H	92	96, *S*	$PhCH_2CH_2$	$SiMe_3$	92	90, *R*
c-C_6H_{11}	Ph	83[b]	86[b], *S*	1-Adamantyl	H	80	95, *R*
Me	Ph	80	71, *S*	1-Adamantyl	H	71[a]	95[a], *R*
Et	Ph	84	88, *S*	1-Adamantyl	$SiMe_3$	70	97, *R*
n-C_6H_{13}	Ph	73	88, *S*	1-Adamantyl	$SiMe_3$	75[a]	95[a], *R*
i-Pr	Ph	85	94, *S*	c-C_6H_{11}	H	60	90, *R*
				c-C_6H_{11}	$SiMe_3$	65	93, *R*

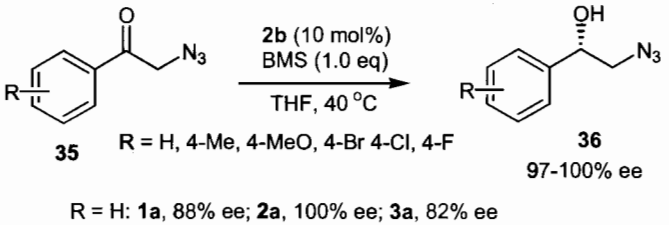
a *ent*-**3b** (20 mol%); **b** **2b** (50 mol%)



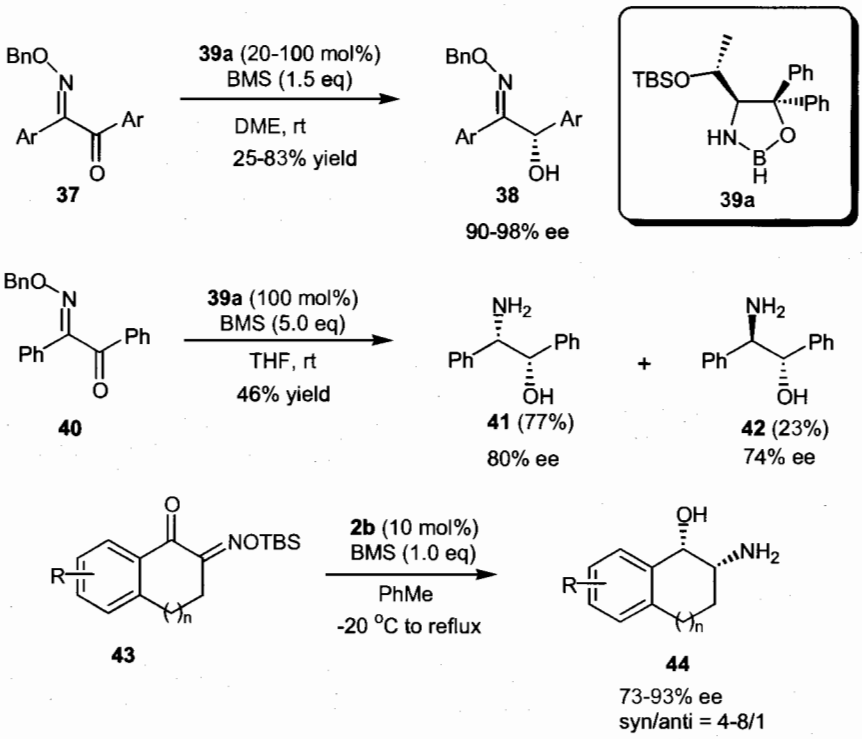
Scheme 11.11 Remote steric effect of substrate and *B*-substituent on enantioselection in the **2**-catalyzed reduction of an α,β-ynone.

11.3.5.6 α-Azido and Imino Ketones

Asymmetric reduction of α-azidoacetophenone derivatives (**35**) using various OABs as catalyst has been reported [71]. Of the OABs examined, **2b** provided the corresponding 2-azido-1-arylethanols (**36**) with very high enantioselectivities (Scheme 11.12) [71]. Reduction of 1,2-diaryl-2-benzyloxyiminoethanone (**37**) with 1.5 equiv. of BMS in the presence of 100 mol% of **39a** in DME at room temperature provided the corresponding α-imino alcohols (**38**) with very high enantioselectivities (Scheme 11.13) [72a]. In this reduction, the use of catalytic amounts of **39a** decreased both the yields and the enantioselectivities. When α-imino ketone (**40**) was reduced with 5 equiv. of BMS, a syn/anti mixture of 1,2-amino alcohols (**41**:**42** = 77:23) was obtained with good enantioselectivity. Similar reduction of cyclic α-imino ketones **43** provided α-amino alcohols **44** with good enantioselectivities [72c].



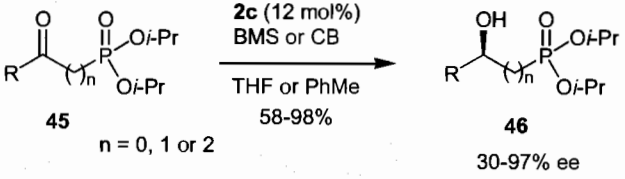
Scheme 11.12 OAB-catalyzed reduction of α-azidomethyl aryl ketones.



Scheme 11.13 OAB-catalyzed reduction of α-imino ketones.

11.3.5.7 α-, β- and γ-Keto Phosphates

The 2c-catalyzed reduction of α-, β- and γ-ketophosphonates 45 using CB as the borane reagent provided the corresponding hydroxyphosphonates 46 with moderate-to-high enantioselectivities. The reduction is also effective for β and γ analogues (Scheme 11.14) [73].

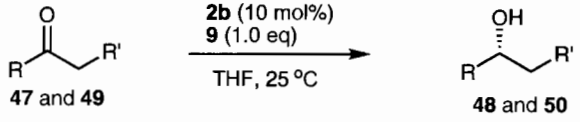


Scheme 11.14 2c-catalyzed reduction of keto phosphates.

11.3.5.8 β-Keto Sulfides and Sulfones

Optically active β-hydroxy sulfides **48** and sulfones **50** are extremely useful chiral building blocks because the α-carbon atom can be further functionalized and the sulfinyl and sulfonyl groups can be cleaved easily without racemization of the chiral center. Recently, Cho and co-workers reported highly effective syntheses for these compounds with excellent enantioselectivities by the **2b**-catalyzed borane reduction of β-keto sulfides **47** and sulfones **49** using EIANB (**9**) as the borane reagent (Table 11.9). The reduction is very effective for both aromatic and hindered aliphatic analogues [74, 75].

Table 11.9 Reduction of β-ketosulfides and β-ketosulfones.

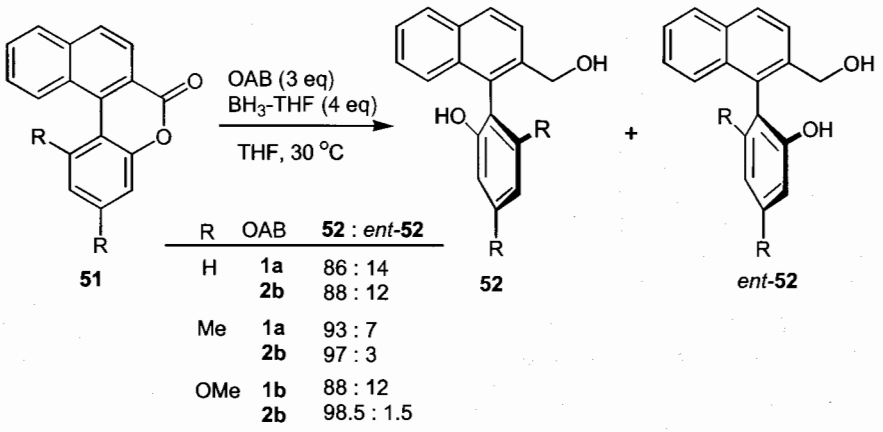


47,48: R = aryl or alkyl, R' = S*p*-tolyl
49,50: R = aryl or alkyl, R' = SO_2*p*-tolyl

48				50			
R	% ee	R	% ee	R	% ee	R	% ee
Ph	97	2-Naph	99	Ph	>99	2-Naph	>99
4-MeC_6H_4	99	2-Furyl	97	4-MeC_6H_4	98	2-Furyl	97
4-MeC_6H_4	99	Et	73	4-$MeOC_6H_4$	98	Et	73
3-ClC_6H_4	99	*n*-C_7H_{15}	74	4-ClC_6H_4	99	*n*-$C_{11}H_{23}$	87
4-ClC_6H_4	>99	*i*-Pr	88	4-FC_6H_4	98	*t*-Bu	99
4-FC_6H_4	>99	*t*-Bu	99	4-$NO_2C_6H_4$	98	*c*-C_6H_{11}	>99
4-$NO_2C_6H_4$	>99	*c*-C_6H_{11}	99				

11.3.6
Atropo-enantioselective Reduction

Bringmann and co-workers have reported highly efficient atropo-enantioselective reduction using OABs as chiral inducers to give one atropisomer with high enantioselectivities [76]. For example, the reduction of biaryl lactones **51** with BH_3·THF (4 equiv.) in the presence of **2b** (3 equiv.) in THF at 30 °C provided chiral biaryl alcohol **52** with up to 97% ee (Scheme 11.15).

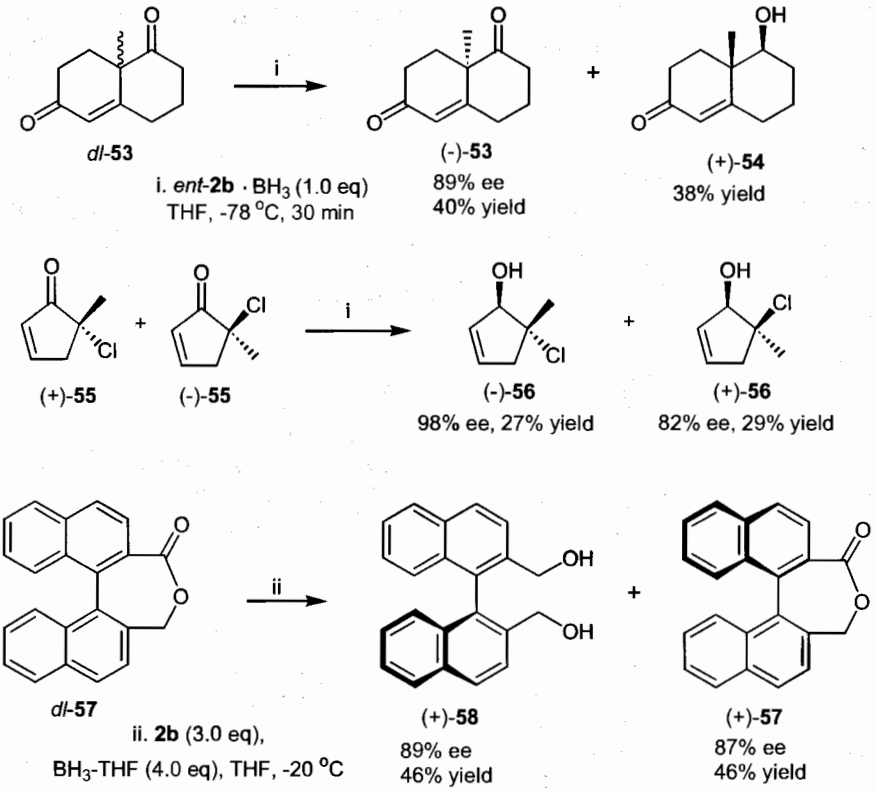


R	OAB	**52** : *ent*-**52**
H	**1a**	86 : 14
	2b	88 : 12
Me	**1a**	93 : 7
	2b	97 : 3
OMe	**1b**	88 : 12
	2b	98.5 : 1.5

Scheme 11.15 OAB-induced atropo-enantioselective reduction of biaryl lactones.

11.3.7
Kinetic Resolution of Racemic Ketones and Biaryl Lactones

In a particularly striking example of the broad applicability of OAB methodology, racemic ketones and biaryl lactones have been resolved kinetically to provide the corresponding ketones and lactones with high enantioselectivities [77–79]. Reduction of a racemic ketone **53** using *ent*-**2b**·BH_3 (0.6 equiv.) in THF at –78 °C for 30 min provided (+)-**54** in 38% yield, leaving unchanged (–)-**53** with 89% ee in 40% yield (Scheme 11.16) [77]. Reduction of racemic ketone **55** under identical conditions, followed by oxidation of each of the product chiral alcohols **56** with PCC, provided (–)-**55** (98% ee) and (+)-**55** (82% ee) [78]. Similarly, kinetic resolution of racemic 7-membered biaryl lactone **57** with BH_3·THF (4.0 equiv.) in the presence of **2b** (3.0 equiv.) in THF at –20 °C provided (+)-**57** (87% ee, 46% yield) [79].



Scheme 11.16 Kinetic resolution of racemic ketones and biaryl lactones via **2b**-induced enantioselective reduction.

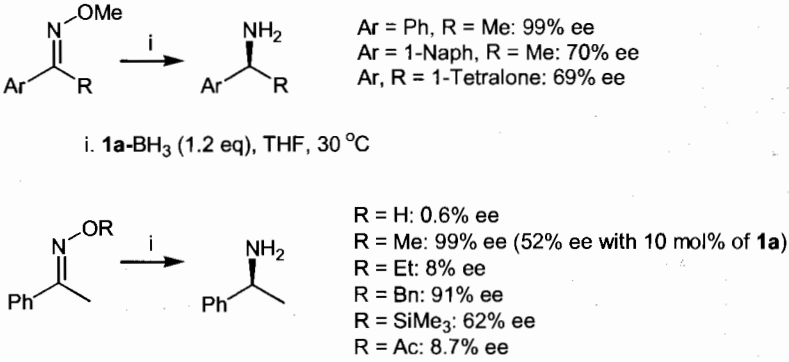
11.4
Asymmetric Reduction of Prochiral Ketimines

In contrast to the numerous known asymmetric ketone reductions, only limited success has been achieved in the reduction of ketimines. This is due to the low electrophilicity of the imine carbon and rapid equilibrium between the *E* and *Z* isomers [80]. In addition, most chiral Lewis acids, including OABs, are trapped by the basic nitrogen atoms of imines and/or product amines, leading to a decreased catalytic effect.

11.4.1
Ketoxime Derivatives

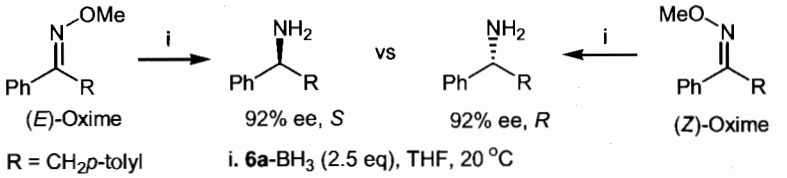
Itsuno and co-workers reported the successful asymmetric reduction of aromatic ketone oxime *O*-alkyl ethers with 1.2 equiv. of **1a** generated in situ from (*S*)-diphenyl valinol and excess borane·THF to produce the corresponding amines in 69–99% ee

[4b]. In the reduction, the oxime provided very low enantioselectivity, and the corresponding *O*-trimethylsilyl ether and acetate afforded moderate enantioselectivities (Scheme 11.17).



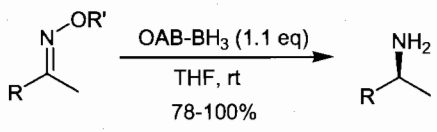
Scheme 11.17 **1a**-induced borane reduction of ketoxime derivatives.

The same authors also found the catalytic effect of **1a** in the reduction of acetophenone oxime *O*-methyl ether, showing that the use of 10 mol% of **1a** afforded product amine with 52% ee [81]. Polymer-supported OABs were also very effective for the same reduction to give (*S*)-1-phenylethylamine with 99% ee [31]. Interestingly, the absolute configurations of the amines formed depend on the geometry of the oxime ethers: the *E* oxime led to the *S* amine, while the *Z* oxime gave rise to the *R* amine (Scheme **11.18**) [82].



Scheme 11.18 Effect of oxime ether geometry on enantioselection.

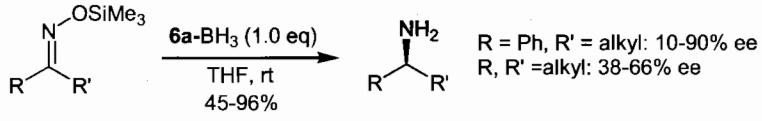
Based on a comparative study for asymmetric reduction of oxime ethers of acetophenone and 2-heptanone using different classes of OABs, such as **1a**, **2a**, and **6a**, Cho and Ryu reported the 6a-induced borane reduction of ketoxime *O*-trimethylsilyl ethers in moderate to good enantioselectivities (Scheme 11.19) [83a, b]. Similarly, benzylic amine derivatives were obtained with high enantioselectivities by stoichiometric reduction of oxime ethers using *ent*-**6a**-BH_3 or **1a**-BH_3 (Scheme 11.20) [84–86].



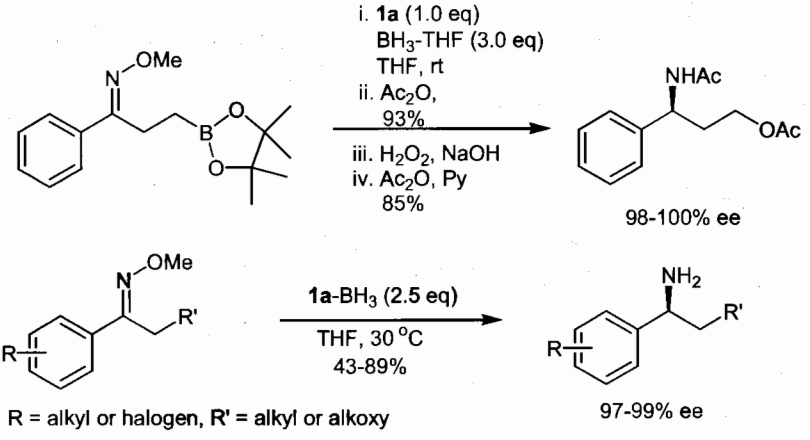
59: R = Ph, R' = Me
60: R = Ph, R' = $SiMe_3$
61: R = n-C_5H_{11}, R' = Me
62: R = n-C_5H_{11}, R' = $SiMe_3$

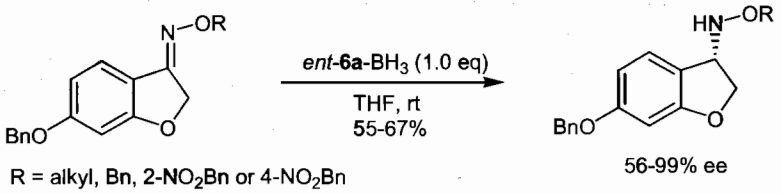
OAB	59	60	61	62
1a	99 (52)*	62	43	10
2a	86 (58)*	40	34	13
6a	58	90	7	40

*OAB (10 mol%)



Scheme 11.19 OAB-induced reduction of ketoxime ether derivatives.



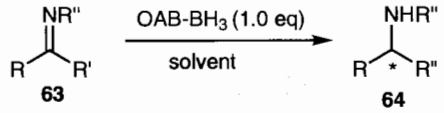


Scheme 11.20 Preparation of optically active benzylamine derivatives via OAB-induced reduction of oxime ethers.

11.4.2
N-Substituted Ketimines

Cho and Chun reported an effective stoichiometric reduction of aromatic ketone *N*-phenylimines **63** using **1a**·BH_3 or **2a**·BH_3 to give the desired *N*-phenylamine **64** with good enantioselectivities (Table 11.10) [87]. The reduction was also effective when 0.1 equiv of **1a** or **2a** was used (runs 2 and 4). BH_3·THF as borane reagent in this reduction led to the *R* amine, whereas CB furnished the *S* amine (runs 8 and 9) [88]. For *N*-alkyl imine analogues, the reduction of *N*-*tert*-butyl imine of acetophenone provided 80% ee (run 12). However, reductions of other *N*-alkyl imine derivatives of the same ketone (runs 10, 11, 13 and 17) and *N*-phenyl or *N*-alkyl imine derivatives of

Table 11.10 Reduction of prochiral *N*-substituted ketimines.



63 **64**

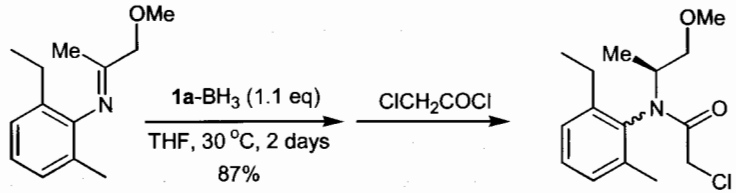
Run No	63			OAB (eq)	Solvent	Temp (°C)	64	
	R	R'	R''				Yield (%)	% ee
1	Ph	Et	Ph	**1a** (1.0)	THF	30	97	87, *R*
2	Ph	Et	Ph	**1a** (0.1)	THF	30	95	66, *R*
3	Ph	Et	Ph	**2a** (1.0)	THF	25	96	78, *R*
4	Ph	Et	Ph	**2a** (0.1)	THF	25	92	70, *R*
5	Ph	*n*-Pr	Ph	**1a** (1.0)	THF	30	97	66, *R*
6	Ph	*i*-Pr	Ph	**1a** (1.0)	THF	30	96	71, *S*
7	Ph	Me	Ph	**1a** (1.0)	THF	30	98	73, *R*
8	Ph	Me	Ph	**2b** (0.1)	THF	30	69	87, *R*
9	Ph	Me	Ph	**2b** (0.1)[a]	THF	30	98	47, *S*
10	Ph	Me	*n*-C_7H_{15}	**1a** (1.0)	THF	30	96	52, *R*
11	Ph	Me	*c*-C_6H_{11}	**1a** (1.0)	THF	30	93	43, *R*
12	Ph	Me	*t*-Bu	**1a** (1.0)	THF	30	90	80, *R*
13	Ph	Me	Bn	**1a** (1.0)	THF	30	98	46, *R*
14	Et	Me	Ph	**1a** (1.0)	THF	30	86	9.4
15	Et	Me	Bn	**1a** (1.0)	THF	30	88	24
16	*i*-Pr	Me	Bn	**1a** (1.0)	THF	30	89	14
17	Ph	Me	Me	**1a** (1.0)	THF	0	58	38, *S*
18	Ph	Me	Me	**2a** (1.0)	toluene	0	60	74, *S*
19	*i*-Pr	Me	Me	**1a** (1.0)	THF	0	78	13
20	*i*-Pr	Me	Me	**2a** (1.0)	toluene	0	71	60
21	*t*-Bu	Me	Me	**1a** (1.0)	THF	0	55	40
22	*t*-Bu	Me	Me	**2a** (1.0)	toluene	0	85	5
23	-$(CH_2)_4$-		Me	**2a** (1.0)	toluene	0	92	50
24	Ph	Me	TBDMS	**3a** (2.0)	CH_2Cl_2	–10	33	79, *R*
25	Ph	Me	TBDMS	**5a** (2.0)	CH_2Cl_2	–10	71	50, *S*

a CB was used as borane reagent.

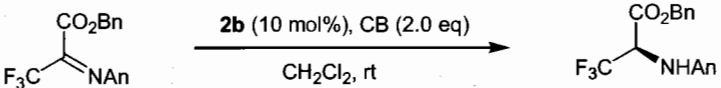
aliphatic ketones were less effective (runs 14–16, 19, and 21–23) [87, 89]. Reduction of acetophenone *N*-*tert*-butyldimethylsilylimine using 3a or 5a under stoichiometric conditions provided the desired amine in good yields, but with moderate enantioselectivities (runs 24 and 25) [90]. Such OAB-induced asymmetric reductions of ketimines have been applied effectively to the asymmetric synthesis of the herbicide metolachlor (**65**) [91], 3,3,3-trifluoroalanine (**66**) [92], a chiral benzodiazepine drug (**67**) [93] and a C_2-symmetric 1,2-diamine (**68**) [94] (Scheme 11.21).

11.5
Summary and Conclusions

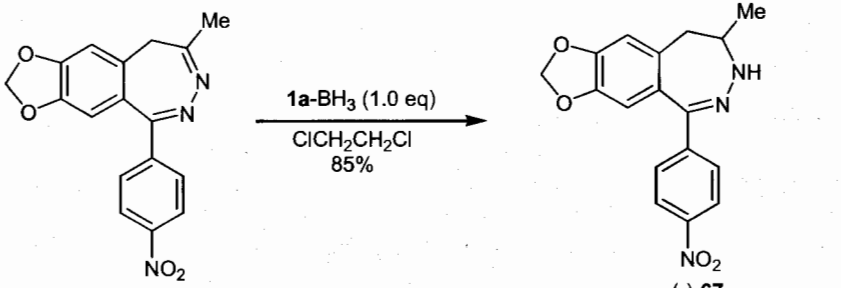
The discovery of OAB-catalyzed reductions of ketones provides an impetus for asymmetric reduction, because the transformation furnishes high enantioselectivity with predictable configurations even in the presence of only 2 mol% of OAB. This catalytic reduction is very effective for not only most aryl alkyl ketones but also for various functionalized ketones, such as heterocyclic ketones, α-halo- and sulfonyloxy ketones, α-hydroxy ketones, diketones, α-keto acetals or thioketals, α,β-enones and ynones, α-azido ketones, *meso*-imides, keto esters, keto phosphates, β-keto sulfides and sulfones, and biaryl ketones and lactones. However, the method shows poor enantioselection in the reduction of unhindered aliphatic ketones, where there is not enough steric bias. In addition, there are few reported examples of the asymmetric reduction of prochiral ketimine derivatives using this methodology. Effective asymmetric reduction of ketones having similar steric bias and ketimine derivatives remain a challenging problem.



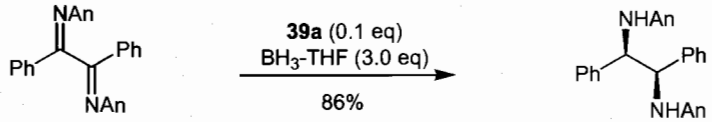
65
62% ee



66
98-100% ee



(-)-**67**
70% ee
>98% ee from recrystallization



An = 4-MeOPh

chiral/meso = 95/5

68
99% ee

Scheme 11.21 Applications of the OAB-induced reduction of ketimines.

Acknowledgments

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12
Boronic Acid-based Receptors and Sensors for Saccharides

Tony D. James

This chapter is dedicated to Professor Seiji Shinkai on the occasion of his 60th birthday

"The idea is to try to give all the information to help others to judge the value of your contribution; not just the information that leads to judgment in one particular direction or another" Richard Feynman (1918–1988)

12.1
Introduction

The chemistry of saccharides is of paramount importance to a wealth of biological functions within nature. By providing the building blocks for processes ranging from the production of metabolic energy through to tissue recognition, saccharides are the focus of a vast body of research aimed at understanding and mimicking their specific role and function at a cellular level [1].

Saccharides and related molecular species are involved in the metabolic pathways of living organisms, therefore, the detection of biologically important sugars (D-glucose, D-fructose, D-galactose, etc.), is vital in various medicinal and industrial contexts. The recognition of D-glucose is of particular interest, since the breakdown of D-glucose transport in humans has been correlated with several diseases: renal glycosuria [2, 3], cystic fibrosis [4], diabetes [5, 6] and also human cancer [7]. Clear evidence exists that tight control of blood sugar levels in diabetics sharply reduces the risk of the debilitating long-term complications associated with this autoimmune disease [8]. Industrial applications of saccharide detection range from the monitoring of fermenting processes to establishing the enantiomeric purity of synthetic drugs.

Current enzymatic detection methods of sugars offer specificity for only a few saccharides; additionally, enzyme based sensors are unstable under harsh conditions. Synthetic systems have been developed using hydrogen-bonding interactions for the purposes of recognition and binding of saccharides. However, in aqueous systems neutral guests may be heavily solvated. As of yet there has been no designed, hydrogen bonding, monomeric receptor that can compete effectively with bulk water for low concentrations of monosaccharide substrates [9].

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Stable boronic acid based saccharide receptors offer the possibility of creating designer saccharide sensors that can be selective and sensitive for any chosen saccharide. The recognition of saccharides by boronic acids has a unique place in supramolecular chemistry. The pair-wise interaction energy is large enough to allow single-point molecular recognition, and the primary interaction involves the reversible formation of a pair of covalent bonds (rather than non-covalent attractive forces). Despite a long history, the first structural and quantitative binding constant data were reported in the 1950s [10–12], and the structure of the boronic acid–saccharide complexes in aqueous solution continues to be discussed [13–15]. There is general agreement that boronic acids covalently react with 1,2 or 1,3 diols to form five- or six-membered cyclic esters. The adjacent rigid *cis*-diols of saccharides form stronger cyclic esters than simple acyclic diols such as ethylene glycol. With reducing saccharides the choice of diol used in the formation of a cyclic ester is complicated by the possibility of pyranose to furanose isomerization of the saccharide moiety (Figure 12.1). Lorand and Edwards first determined the selectivity of phenylboronic acid towards saccha-

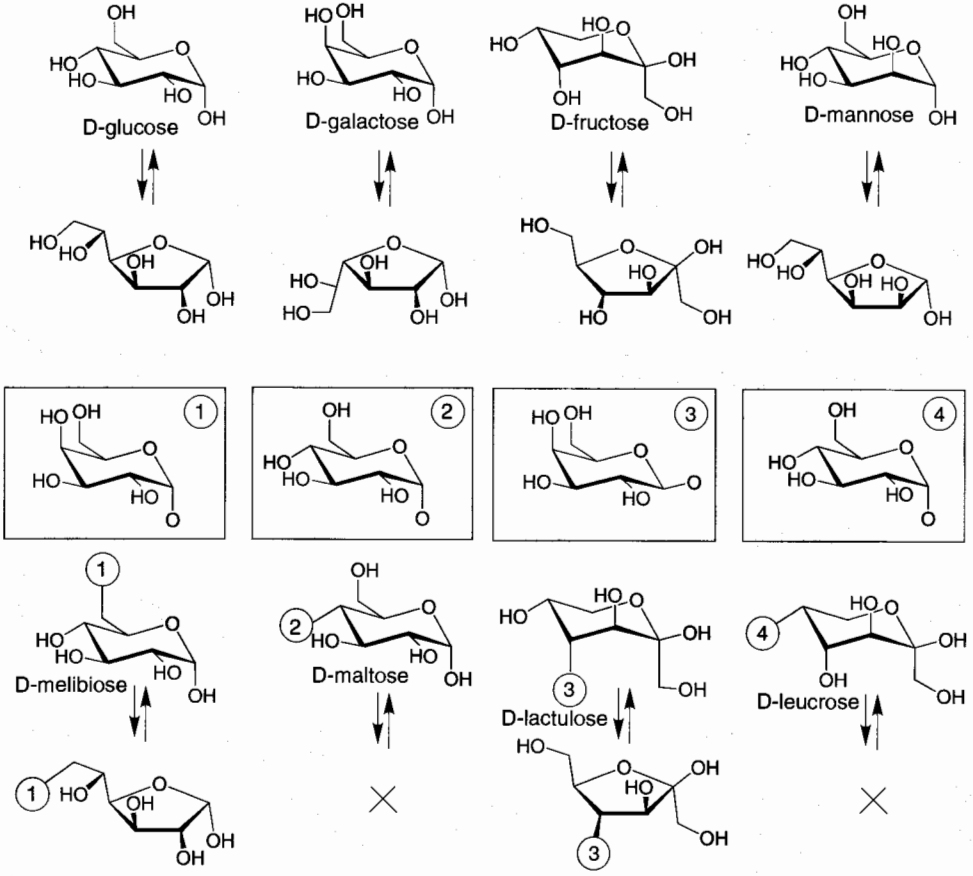
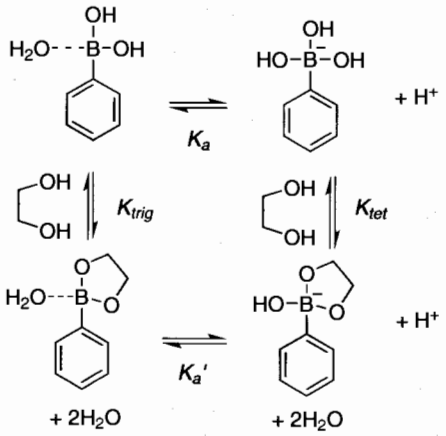


Figure 12.1 Pyranose to furanose isomerization for selected saccharides.

rides and this selectivity order seems to be retained by all monoboronic acids (D-fructose > D-galactose > D-glucose) [12].

Equilibria involved in the phenylboronate binding of a diol are conventionally summarized as a set of coupled equilibria (Scheme 12.1). In aqueous solution phenylboronic acid reacts with water to form the boronate anion plus a hydrated proton, thereby defining an acidity constant K_a. [Scheme 12.1 shows an explicit water molecule "coordinated" to the trigonal boronic acids. There is undoubtedly water in rapid exchange on the Lewis acidic boron in the same way that hydrated Lewis acidic metal ions exchange bound water. A good analogy is Zn^{2+} (aq), which ionizes in water to give a $pK_a = 8.8$, i.e. $Zn{-}OH_2 \rightarrow Zn{-}OH + H^+$ [16]].



Scheme 12.1

The formation of a diol boronate complex, defined by K_{tet}, formally liberates two equivalents of water, but this stoichiometric factor is usually ignored as a constant in dilute aqueous solution. In a formal sense, phenylboronic acid could also bind diols to form a trigonal complex (K_{trig}), and this species would itself act as an acid according to K_a'. The "acidification" of solutions containing phenylboronic acid and diols is always discussed in terms of the trigonal complex being a stronger acid than the parent phenylboronic acid, i.e. $K_a' > K_a$ [17]. Since all the equilibria are coupled this results in the stability constant (K_{tet}) of the tetrahedral complex being greater than the stability constant (K_{trig}) of the trigonal complex. There are kinetic differences as well: the rate of ester formation between a tetrahedral boronate and a diol is more rapid by a factor of $\geq 10^6$ than between a trigonal boronic acid and a diol [18, 19].

The simplest way to think about the pK_a of boronic acids is to consider a solvent water molecule associated with the sp^2 boronic acid, at high pH the water is deprotonated and forms a tetrahedral sp^3 boronate. On saccharide binding and formation of a cyclic boronate ester the pK_a of the boronic acid is lowered, or in other words the 'ester' is more acidic than the 'acid'. The enhanced acidity is due to a bond angle compression on formation of a cyclic boronate ester. Boronic acids have a 120° (sp^2) bond angle but on the formation of a cyclic ester the bond angle is reduced to 108°. Obvi-

ously, this compression of the bond angle makes the change in hybridization from sp^2 to sp^3 on deprotonation occur more readily.

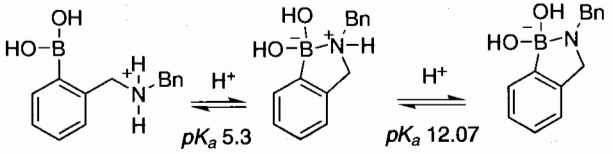
However, these four coupled equilibria from Scheme 12.1 are not the full story. Boronic acids readily form stable complexes with buffer conjugate bases (phosphate, citrate and imidazole) [20]. In fact, both binary boronate–X complexes are formed with Lewis bases (X), as well as ternary boronate–X–saccharide complexes. In some cases, these previously unrecognized species persist into acidic solution and under some stoichiometric conditions they can be the dominant components of the solution. These complexes suppress the boronate and boronic acid concentrations, leading to a decrease in the measured apparent formation constants (K_{app}). As a consequence, the scope of the "simple" diol–boronate recognition system is greatly expanded over the simple picture of Scheme 12.1.

When boronic acid based saccharide sensors are monitored, the "out-put" is translated into a measured conditional or apparent stability constant (K_{app}). These conditional or apparent constants may be suitable for developing useful systems, so long as any competing equilibria with the buffer do not overwhelm the system. In any case, it is simple to inspect the influence of the buffer components to allow a judicious choice of buffer concentration and pH to generate an optimal signal from the system under study. More importantly so long as we are aware of the origin of the measured constant (K_{app}) it will be possible to translate these constants back into the constants associated with the four coupled equilibria shown in Scheme 12.1. [In some cases the model used to analyze the data may be incomplete and the derived K_{app} will then be a composite parameter. This commonly occurs in spectroscopic determinations where the measured signal is a sum of several competing species. However, a complete model will always allow a direct relationship of K_{app} to the fundamental equilibria of Scheme 12.1.]

Formation of a saccharide complex at neutral pH is essential if practical boronic acid based sensors are to be developed. Since pK_a' is 1–2 units lower than pK_a, the boronic acid–saccharide complex will only exist in significant amounts at neutral pH if the pK_a of the boronic acid itself is ≤ 7. The pK_a of phenyl boronic acid has been reported as 8.8 [21–23]; hence phenyl boronic acid requires basic aqueous conditions to form strong complexes. Therefore, to realize strong binding at neutral pH the pK_a of the boronic acid must be lowered. This can be achieved by incorporating electron-withdrawing groups onto the aromatic moiety, e.g. 4-carboxy-3-nitrophenylboronic acid has a pK_a of 7.0 [23]. Another approach, pioneered by Wulff, employs a neighboring aminomethyl substituent [24]. The acidity constant for the second stepwise protonation in water of these *o*-aminomethylarylboronic acids has been determined as 5.3 [20, 24, 25]. Using ^{11}B NMR Anslyn has shown that the monoprotonated species was tetrahedral at boron [25]. Equilibria for these *o*-aminomethylboronic acids can thus be formulated as shown in Scheme 12.2.

A growing number of excellent reviews cover the use of boronic acids in the development of saccharide receptors [17, 26–33].

The present chapter provides an overview of current and future directions in the development of saccharide sensors. Two components are required for a sensor: a selective interface and a read-out mechanism. This chapter will concentrate on systems



Scheme 12.2

where the read-out units are fluorescent, colorimetric or electrochemical. The next step is to incorporate a better interface so that selectivity can be controlled. Factors that will affect saccharide selectivity are the number and type of receptor units and the orientation and position of these receptor units within the sensor. More boronic acid units should, if positioned correctly, improve selectivity for particular saccharides, e.g. a larger spacing between these units will favor polysaccharides. Also, additional non-boronic acid binding units can be incorporated to allow selectivity amongst derivatives such as amino, carboxy and phosphorylated saccharides.

12.2 Fluorescence

Fluorescent sensors for saccharides are of particular practical interest. This is in part due to the inherent sensitivity of the fluorescence technique. Only small amounts of a sensor are required (typically 10^{-6} M), offsetting the synthetic costs of such sensors. Fluorescent sensors have also found applications in continuous monitoring using fiber optics [34] and intracellular mapping using confocal microscopy [35].

12.2.1 Internal Charge Transfer (ICT)

The first fluorescent sensors for saccharides were based on fluorophore appended boronic acids. Czarnik showed that 2- and 9- anthrylboronic acid [36, 37] (**1** and **2**) could be used to detect saccharides (Figure 12.2). With these systems, the negatively charged boronate has a lower fluorescence than the neutral boronic acid. Since the pK_a of a boronic acid is lowered on saccharide binding, the fluorescence of these systems at a fixed pH decreases when saccharides are added. The observed stability constant (K_{app}) for **1** was 270 M^{-1} with D-fructose at pH 7.4 (phosphate buffer).

Aoyama has also shown that 5-indolylboronic acid (**3**) undergoes fluorescence quenching upon complexation with oligosaccharides [38]. The stability constants of monosaccharides followed the trend observed by Lorand and Edwards [12]; however, higher oligomers of saccharides enjoyed increased stabilization relative to lower oligomers due to a secondary interaction with the indole N–H. The observed stability constants (K_{app}) for **3** were D-fructose 630 M^{-1}, D-glucose 7.1 M^{-1} and D-melibiose 58 M^{-1} in water at pH 9.

Anthrylboronic acids (**1**, **2**) used by Czarnik display only a small fluorescence change. By screening eight aromatic boronic acids it was shown that **4** and **5** produce

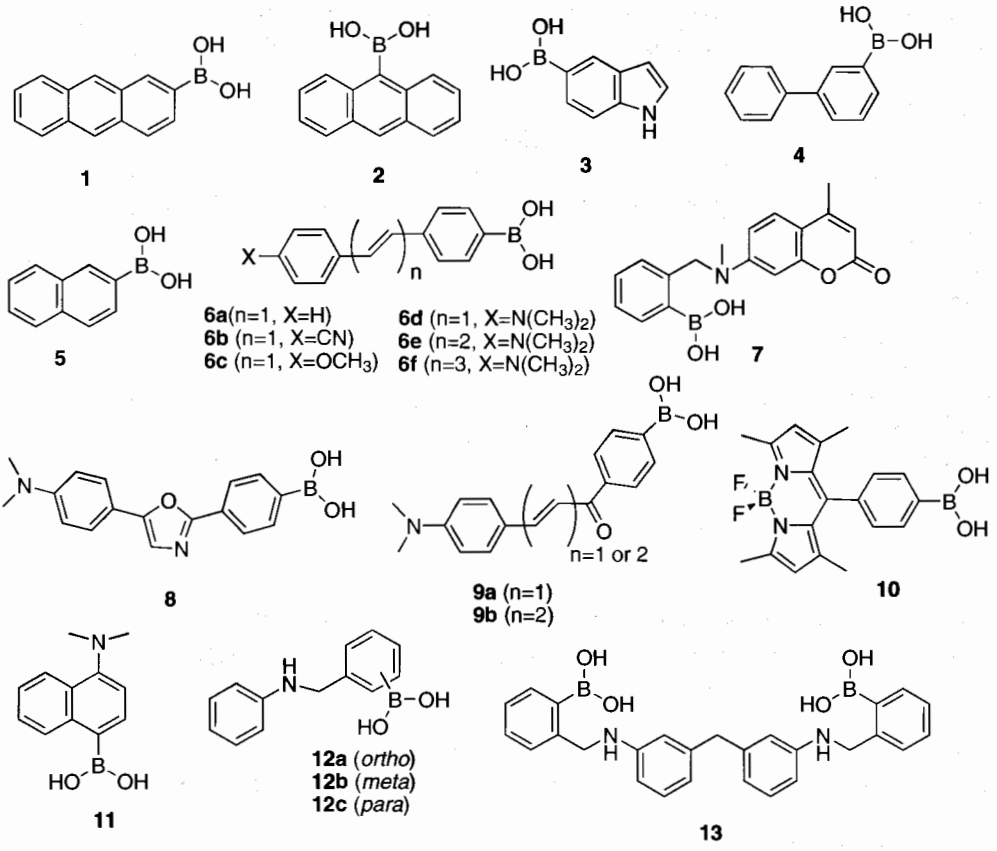


Figure 12.2 Internal charge transfer (ICT) fluorescence sensors.

much larger fluorescence responses on saccharide binding and as such are more suitable candidates for saccharide detection [39, 40].

Originally, photoinduced electron transfer (PET) was thought to be the source of the fluorescence quenching from the boronate anion for the systems described above. A more reasonable explanation, though, comes from the investigation of stilbene boronic acid **6a** by Shinmori [41] and the detailed investigation of several stilbene and longer polyene boronic acids (**6a–f**) by Lakowicz [42, 43]. The neutral form of the boron group acts as an electron-withdrawing group, while the anionic form acts as an electron-donating group. Hence, the changes in electronic properties of the boron group cause the spectral changes of the fluorophore. The observed stability constants (K_{app}) for **6a–f** ranged from 1538 to 294 M^{-1} for D-fructose and 90 to 10.2 M^{-1} for D-glucose in 2:1 (v/v) water–methanol at pH 8.0 (phosphate buffer).

Accordingly, in this chapter the original fluorescence systems have been classified as internal charge transfer (ICT) fluorophores where the acceptor is the boronic acid (these systems have no defined donor).

Sandanayake et al. made the first systematic attempt to couple a donor and acceptor in the construction of an ICT system using the coumarine boronic acid **7** [44]. Here both fluorescence intensity and wavelength are affected since the nitrogen is directly connected with the chromophore. Sadly, this system shows small shifts in intensity and wavelength, in spite of its clever molecular design. The observed stability constant (K_{app}) for **7** was 27 M^{-1} for D-fructose in 1:1 methanol–water.

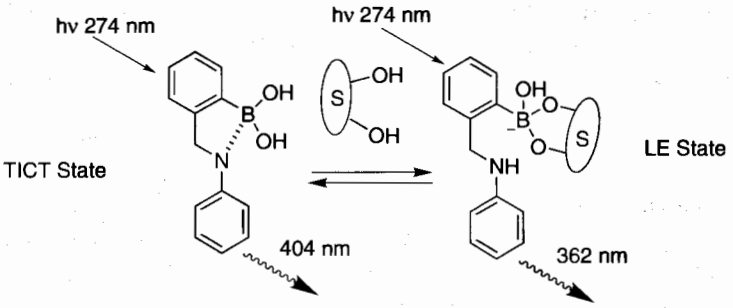
Lakowicz quickly recognized the importance of stilbene boronic acid **6d** and has since prepared several analogous ICT fluorophore systems, including oxazoline **8** [45], chalcones **9a,b** [46] and boron-dipyrromethene (BODIPY) **10** [47]. The observed stability constants (K_{app}) for **8** were 526 M^{-1} for D-fructose and 27 M^{-1} for D-glucose in 2:1 (v/v) water–methanol at pH 7.0 (phosphate buffer). K_{app} for **9a,b** were 400, 476 M^{-1} for D-fructose and 29, 33 M^{-1} for D-glucose in 2:1 (v/v) water–methanol at pH 6.5 (phosphate buffer). K_{app} for **10** were 1000 M^{-1} for D-fructose and 13.7 M^{-1} for D-glucose in water at pH 7.5 (phosphate buffer).

Oxazoline **8** and chalcone **9a,b** systems produce large fluorescence changes; however, the BODIPY system displays only a small change in fluorescence. Although the BODIPY system **10** did not work particularly well, this class of fluorophore requires further exploration. The BODIPY chromophore possess many advantages as a fluorescent probe: e.g. it possess high extinction coefficients, high fluorescence quantum yields, good photostability, a narrow emission band and their building block synthesis allows the development of many different analogues showing emission maxima from 500 to 700 nm. Long-wavelength fluorescent probes for D-glucose are highly desirable for transdermal D-glucose monitoring and/or for measurements in whole blood. In addition, narrow emission bands are desirable for high signal-to-noise ratios. Lakowicz and Geddes have demonstrated recently the usefulness of this type of fluorescent sensor by preparing contact lenses doped with **6b, d, e** and **9a, b** to prepare noninvasive monosaccharide sensors [48].

Wang has recently shown that the very simple naphthalene system **11** can produce very large fluorescence changes (41-fold on addition of 50 mM fructose) [49]. The observed stability constants (K_{app}) for **11** were 207 M^{-1} for D-fructose and 4.0 M^{-1} for D-glucose in water at pH 7.4 (phosphate buffer).

James and co-workers have prepared **12a**, a monoboronic acid fluorescent sensor that shows large shifts in emission wavelength on saccharide binding [50]. The dual fluorescence of **12a**, can be ascribed to locally excited (LE) and twisted internal charge transfer (TICT) states of the aniline fluorophore [51]. When saccharides interact with sensor **12a** in aqueous solution at pH 8.21 the emission maxima at 404 nm (TICT state) shifts to 362 nm (λ_{ex} 274 nm, LE state). The band at 404 nm is due to the TICT state of **12a** containing a B–N bond i.e. the lone pair is coordinated with the boron and perpendicular to the π-system. The band at 274 nm (LE state) corresponds to the situation where the B–N bond in **12a** has been broken with formation of the boronate (Scheme 12.3).

When **12b** and **12c** were excited at 240 and 244 nm respectively an emission at 350 nm was observed (excitation at 274 nm resulted in no emission) [51]. Also, when compound **12a** was excited at 244 nm, only emission at 360 nm was observed. In all these cases only the LE state is formed (no B–N bond is possible). The large fluores-



Scheme 12.3 Locally excited (LE) and twisted internal charge transfer (TICT) states of **12a**.

cence enhancements (λ_{ex} 240 or 244 nm) obtained for **12a–c** on the addition of D-fructose, i.e. 15-, 18- and 25-fold, can be attributed to fluorescence recovery of the aniline fluorophore. With these systems, in the absence of saccharides the normal fluorescence of the LE state of the aniline donor is quenched by energy transfer to the phenylboronic acid acceptor. When saccharides are added, a negatively charged boronate anion is formed. Under these conditions energy transfer from the aniline donor is unfavorable and fluorescence recovery of the LE state of the aniline donor is observed. Although these systems may be of limited practical use (aniline is not the best fluorophore), understanding this simple unit may allow the design and development of improved ICT fluorescent systems [50].

K_{app} for **12a–c** were 79, 212, 129 M^{-1}, respectively, for D-fructose and 6.4, 8.7, 6.7 M^{-1} for D-glucose in 52.1 wt% methanol–water at pH 8.21 (phosphate buffer) [51].

James and co-workers then combined the requirements of the signaling unit with those of a D-glucose selective receptor and prepared diboronic acid sensor **13** [52]. K_{app} for **13** were 55 M^{-1} for D-fructose and 140 M^{-1} for D-glucose in 52.1 wt% methanol–water at pH 8.21 (phosphate buffer). The relative stability constants of the diboronic acid **13** to the monoboronic acid **12a** shows how effective appropriate molecular design is at enhancing the D-glucose binding. Cooperative binding of the two boronic acid groups is clearly illustrated by the stability constant differences between the mono- and diboronic acid compounds. The K_{app} of diboronic acid sensor **13** with D-glucose is 14 times greater than with monoboronic sensor **12a**, while K_{app} of diboronic acid sensor **13** with D-fructose is 0.6 times less than monoboronic acid sensor **12a**. This result can be easily explained since D-glucose readily forms 1:1 cyclic complexes with diboronic acids, whereas D-fructose tends to form 2:1 acyclic complexes with diboronic acids [17].

12.2.2
Photoinduced Electron Transfer (PET)

Photoinduced electron transfer (PET) has been widely used as the preferred tool in fluorescent sensor design for atomic and molecular species [53–56]. PET sensors generally consist of a fluorophore and a receptor linked by a short spacer. Changes in

oxidation/reduction potential of the receptor upon guest binding can affect the PET process, creating changes in fluorescence.

The first rationally designed fluorescent PET saccharide sensor, compound **14**, was prepared by James in 1994 [57, 58] (Figure 12.3). Observed K_{app} for **14** were 1000 M^{-1} for D-fructose and 60 M^{-1} for D-glucose in 33.3 wt% methanol–water at pH 7.77 (phosphate buffer) [57]. This fluorescence sensor contains a boronic acid group and an amine group. The boronic acid group is required to bind with and capture saccharides in water. The amine group plays two roles in the system. (1) Boronic acids with a neighboring amine facilitate the binding of saccharides to boronic acids at neutral pH. (2) Fluorescence intensity is controlled by the amine lone pair.

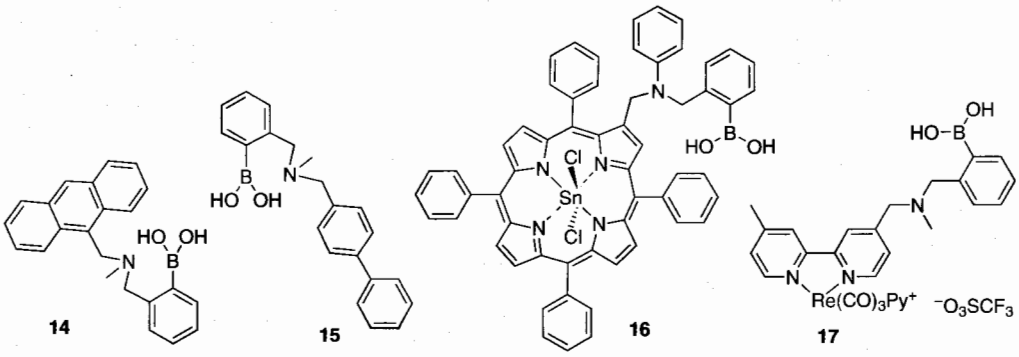
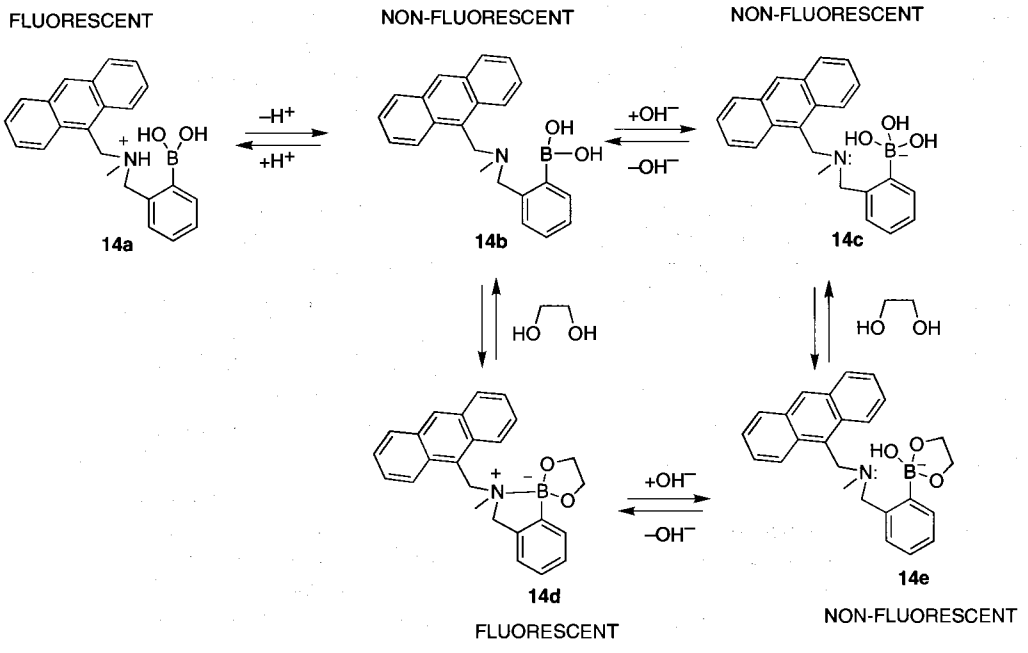


Figure 12.3 Monoboronic acid photoinduced electron transfer (PET) fluorescent sensors.

The change in fluorescence in these systems has been attributed to an increase in the strength of the B–N Lewis acid–Lewis base interaction upon saccharide binding. Wang has recently published an excellent computational exploration on the extent of B–N interactions in similar systems [59]. The calculations predicted B–N distances within the expected range [60] and estimated the interaction energy to be 13 kJ mol^{-1} or less in the absence of solvent [59]. This value agrees with the range of B–N interaction determined by James and co-workers using potentiometric titrations (15–25 kJ mol^{-1}) [20]. These values are vital since the B–N interaction has been used as the basis for many sensing applications using boronic acids. If the interaction were much weaker then the nitrogen would not compete with external bases in solution. Conversely, if it were much stronger, saccharide binding could not disrupt the B–N interaction and no differential signal would develop. The balance of energetics is essential to the application of these systems for sensors, whatever the signalling mechanism [59].

With **14** the 'free' amine reduces the intensity of the fluorescence (quenching by PET). This is the 'off' state of the fluorescent sensor. When sugar is added, the amine becomes coordinatively 'bound' to the boron center. The boron-bound amine cannot quench the fluorescence and hence a strong fluorescence is observed. This is the 'on' state of the fluorescent sensor. The system described above illustrates the basic concept of an 'off-on' fluorescent sensor for saccharides (Scheme 12.4).



Scheme 12.4 Effect of saccharide complexation and pH changes on the fluorescence of monoboronic acid **14**.

Two other systems are worthy of special mention since they differ from that outlined above: The simple monoboronic acid **15** used by James and co-workers, which can selectively signal the furanose form of saccharides [61], and the 'on-off' PET system **16** of Kijima, where steric crowding on saccharide binding breaks the B–N bond found in the 'free' receptor [62].

Cary and Satcher, while attempting to extend the fluorescence emission to longer wavelengths, have prepared the rhenium bipyridine system **17**. This system produces a good fluorescence response to D-glucose in methanol, but fails to produce a response to D-glucose in 1:1 (v/v) methanol–phosphate-buffered saline solution [63]. The failure of this system can probably be traced back to competing equilibria with the buffer overwhelming the system. Kukrer and Akkaya have achieved near-IR fluorescence response to saccharides by using the diboronic acid squarene **18** (Figure 12.4). Sadly, the system only produces an 8% change in fluorescence intensity with added D-glucose [64].

The simple 'off-on' PET system **14** was improved by James with the introduction of a second boronic acid group **19** [57, 65]. K_{app} for **19** were 320 M^{-1} for D-fructose and 4000 M^{-1} for D-glucose in 33.3 wt% methanol–water at pH 7.77 (phosphate buffer) [57, 65]. With **19**, two possible saccharide binding modes can inhibit the electron-transfer process to give higher fluorescence: a 2:1 complex and a 1:1 complex. Due to fortuitous spacing of the boronic acid groups the diboronic acid was selective for D-glucose over other monosaccharides, including D-fructose. This effectively led to

an inversion of the glucose/fructose selectivity for **19** when compared to the monoboronic acid system **14**. Lakowicz has recently demonstrated that these two systems could be used as fluorescence lifetime (the lag time between the emission and excitation) sensors for saccharides [66]. Fluorescence lifetime based sensors are important since the lifetime is an intrinsic property that is not affected by minor optical changes or fluorophore concentration. These lifetime measurements were also able to confirm unequivocally that the boronic acid saccharide interaction is reversible.

Norrild and co-workers have carried out a more detailed investigation of this system to confirm the structure of the bound D-glucose [67]. Norrild was interested in the system since the reported ^{1}H NMR [57, 65] indicated that D-glucose bound to the receptor in its pyranose form. Norrild with Eggert had previously shown that simple boronic acids selectively bind with the furanose form of D-glucose [13]. From ^{1}H NMR observations it was concluded that the diboronic acid initially binds with the pyranose form of D-glucose and over time the bound D-glucose converts into the furanose form.

James and co-workers have used **20** (*R* or *S*) (Figure 12.4) for the chiral recognition of saccharides and sugar acids [68, 69]. Asymmetric immobilization of the amine groups relative to the binaphthyl moiety upon 1:1 complexation of saccharides by D- or L-isomers creates a difference in PET. This difference is manifested in the maximum fluorescence intensity of the complex. Steric factors arising from the chiral binaphthyl building block are chiefly represented by the stability constant of the complex. However, interdependency of electronic and steric factors is not excluded. This new molecular cleft, with a longer spacer unit than the anthracene-based diboronic acid **19**, gave the best recognition for fructose. Chiral recognition of saccharides employing hydrogen bonding by polyhydroxyl molecules has been reported; however, discriminative detection of enantiomers in aqueous media by fluorescence had not been achieved before [9]. In this system, steric factors and electronic factors bimodally discriminate the chirality of the saccharide. Competitive studies with D- and L-monosaccharides show the possibility of selective detection of saccharide enantiomers. The availability of both *R* and *S* isomers of this particular molecular sensor is an important advantage, since concomitant detection by two probes is possible. K_{app} for **20** (*R* or *S*) were 10 000, 5000 M^{-1} for D-fructose and 2000, 2500 M^{-1} for D-glucose in 33.3 wt% methanol–water at pH 7.77 (phosphate buffer).

Linnane et al. have attempted to use the calixarene framework **21** as a core on which to develop novel saccharide selective systems [70]. Observed K_{app} for **21** were 115 M^{-1} for D-fructose and 24 M^{-1} for D-glucose in 33.3 wt% methanol–water at pH 7.77 (phosphate buffer). The calixarene unit has also been used by Matsumoto to develop novel luminescent systems [71]. Although success has been limited with these calixarene systems, the concept of using the versatile calixarene framework upon which to build saccharide selective systems appears to be a good one.

Diboronic acid **22** with a small spacing of the boronic acid groups has been synthesized by James and co-workers and shown to be selective for D-sorbitol [72]. The K_{app} for **22** were 350 M^{-1} for D-sorbitol and 330 M^{-1} for D-fructose in 300:1 (v/v) water–methanol at pH 8.0. Conversely, diboronic acid **23** prepared by Linnane et al. with a larger spacing between the boronic acid groups loses selectivity and sensitivity [73].

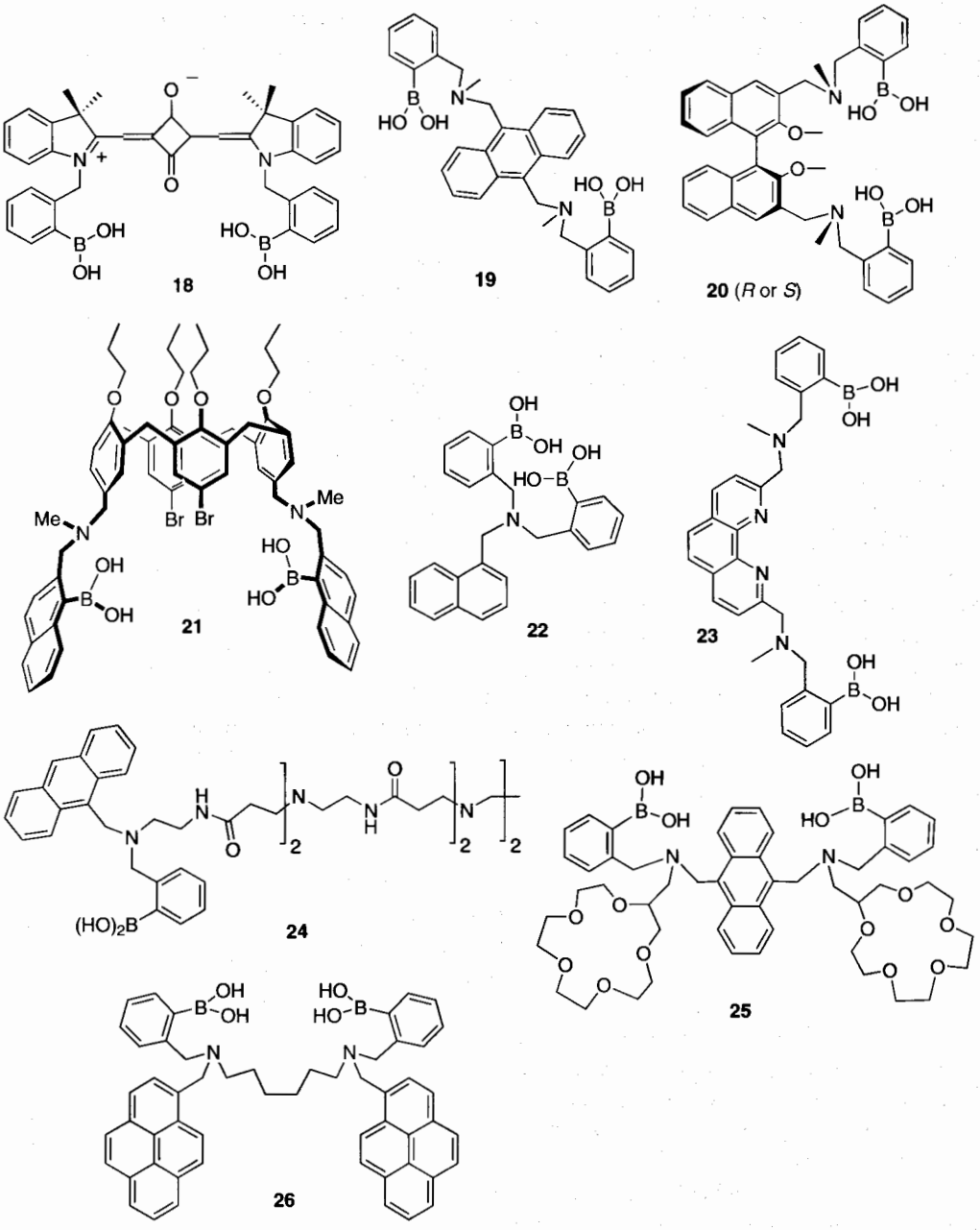


Figure 12.4 Multiboronic acid photoinduced electron transfer (PET) fluorescent sensors.

K_{app} for **23** were 170 M^{-1} for D-fructose and 91 M^{-1} for D-glucose in 33.3 wt% methanol–water at pH 7.77 (phosphate buffer). Dendritic boronic acid **24**, prepared by James, behaves like a saccharide sponge and shows enhanced binding affinities for all monosaccharides [74]. K_{app} for **24** were 16 900 M^{-1} for D-fructose and 740 M^{-1} for D-glucose in methanol.

An allosteric diboronic acid **25** has been prepared by James; with this system formation of a 1:2 metal/crown sandwich causes the release of bound saccharide due to a metal induced conformational change [75].

With sensor **26**, prepared by Sandanayake, the amount of excimer can be correlated directly with the amount of non-cyclic saccharide complex formed [76]. Observed K_{app} for **26** were 2000 M^{-1} for D-glucose and 790 M^{-1} for D-galactose in 33.3 wt% methanol–water. Appleton has found that as the linker length of this system was increased the selectivity for D-glucose was lost [77].

Each of the sensors described above have been designed and synthesized individually. This is a very time and resource intensive approach to sensor design. Consequently, James and co-workers looked for more convergent strategies towards the construction of sensor systems. On inspection of previous sensor molecules they noted that in all cases the receptor unit was constant (*ortho*-aminomethylarylboronic acid). Then, by taking the receptor unit as one module, they realized that new sensors could be constructed using this and other modules. The basic idea was to break sensors into three components; receptor units, spacer units, and read-out units. Their approach can be illustrated by describing the D-glucose selective fluorescence sensor **26**, which contains two boronic acid units (receptors), a hexamethylene unit (D-glucose selective spacer), and a pyrene unit (fluorophore – read-out). Using compound **26** as a model any new saccharide selective sensor requires at least two boronic acid units, one spacer unit, and a "read-out" unit. Two or more boronic acid units as with sensor **26** are required because only through two points binding can saccharide selectivity be controlled. One "read-out" unit is required to report on saccharide binding. Two fluorophores are not required and may be detrimental to an operational sensor since the fluorescence spectra of sensor **26** are complicated by excimer emission due to stacking of the two-pyrene units. Also, a spacer is required, and the choice of spacer is very important since it will determine the selectivity of the sensor. With compound **26** a hexamethylene spacer results in D-glucose selectivity. Based on the above criteria, sensors **27a–f** were designed [78, 79].

Compound **27d** with a hexamethylene linker and pyrene fluorophore displays D-glucose selectivity, whilst systems with longer linker units (**27e, fb**) display enhanced selectivity for D-galactose. [To help visualize the trends in the observed stability constants, the stability constants of the diboronic acid sensors **27** were compared with those of the equivalent monoboronic acid analogues **28**. The relative stability illustrates that selectivity is increased by cooperative binding through the formation of 1:1 cyclic systems. The large enhancement of the relative stability observed for the 1:1 cyclic systems (D-glucose, D-galactose) are clearly contrasted with the small two-fold enhancement observed for the 2:1 acyclic systems (D-fructose, D-mannose).] The K_{app} for **27d** were 784 M^{-1} for D-fructose, 657 M^{-1} for D-galactose and 962 M^{-1} for D-glucose in 52.1 wt% methanol–water at pH 8.21 (phosphate buffer) (Figure 12.5).

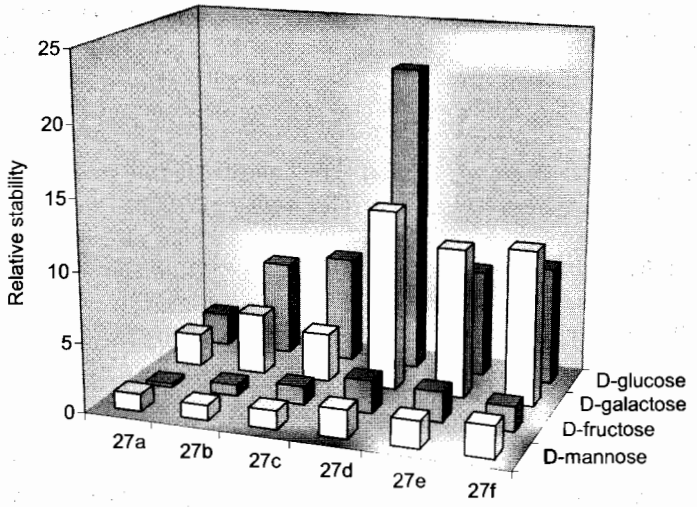


Figure 12.5 Relative stability of **27a–f** compared to **28a** with saccharides.

Having determined the effect of the linker on saccharide selectivity James and co-workers set out to further probe the factors affecting saccharide selectivity The next logical component to vary was the fluorophore or 'read-out' unit of sensors **27d, g–j** where ($n = 6$) (Figure 12.6) [80]. Although not directly involved in saccharide binding, the nature of this unit directly influence both the solvation and steric crowding of the binding site.

Sensors **27d, g** and h show enhanced selectivity for D-glucose over D-galactose; with sensors **27i, j** the selectivity switches from D-glucose to D-galactose. [Trends in the observed stability constants were also visualized by comparison with those of the equivalent monoboronic acid analogues **28**]. These results demonstrate that the choice of the fluorophore is crucial in a PET saccharide sensor with two phenylboronic acid groups, a hexamethylene linker and a fluorophore. Selectivity is fluorophore dependent and careful choice of the fluorophore, such that it complements the polarity of the chosen guest species, is imperative. Observed K_{app} for **27j** were 1068 M^{-1} for D-fructose, 894 M^{-1} for D-galactose and 532 M^{-1} for D-glucose in 52.1 wt% methanol–water at pH 8.21 (phosphate buffer) (Figure 12.7).

Wang and co-workers have also prepared diboronic acid systems with two anthracene fluorophores with variable spacers (**29a–j**) [81, 82]. They demonstrated that **29e** is selective for Sialyl Lewis X [81] and that **29f** is selective for D-glucose [82]. Observed K_{app} for **29f** were 34 M^{-1} for D-fructose, 30 M^{-1} for D-galactose and 1472 M^{-1} for D-glucose in 1:1 (v/v) methanol–water at pH 7.4 (phosphate buffer).

Hall and co-workers have taken the modular approach a step further and employed a solid-phase synthetic approach to optimize structural and electronic properties of boronic acid sensors for oligosaccharides [83]. Through this approach they determined that para electron-withdrawing groups on the boronic acids were beneficial. The approach also allows for the easy introduction of different boronic acid units. Di-

boronic acid sensor **30** has a binding constant of 1870 M^{-1} with D-lactulose, while the unsubstituted diboronic acid has a binding constant of only 315 M^{-1} in 1:1 (v/v) methanol–water at pH 7.8 (phosphate buffer). The research also indicated that saccharides with an isomerizable reducing end capable of forming a rigid furanose ring with *cis*-1,2-diols have higher binding constants. This phenomenon is well known, and the observation also agrees with the recent evaluation of diboronic acids **27a–f** with disaccharides. Amongst these sensors **27d** binds particularly strongly with

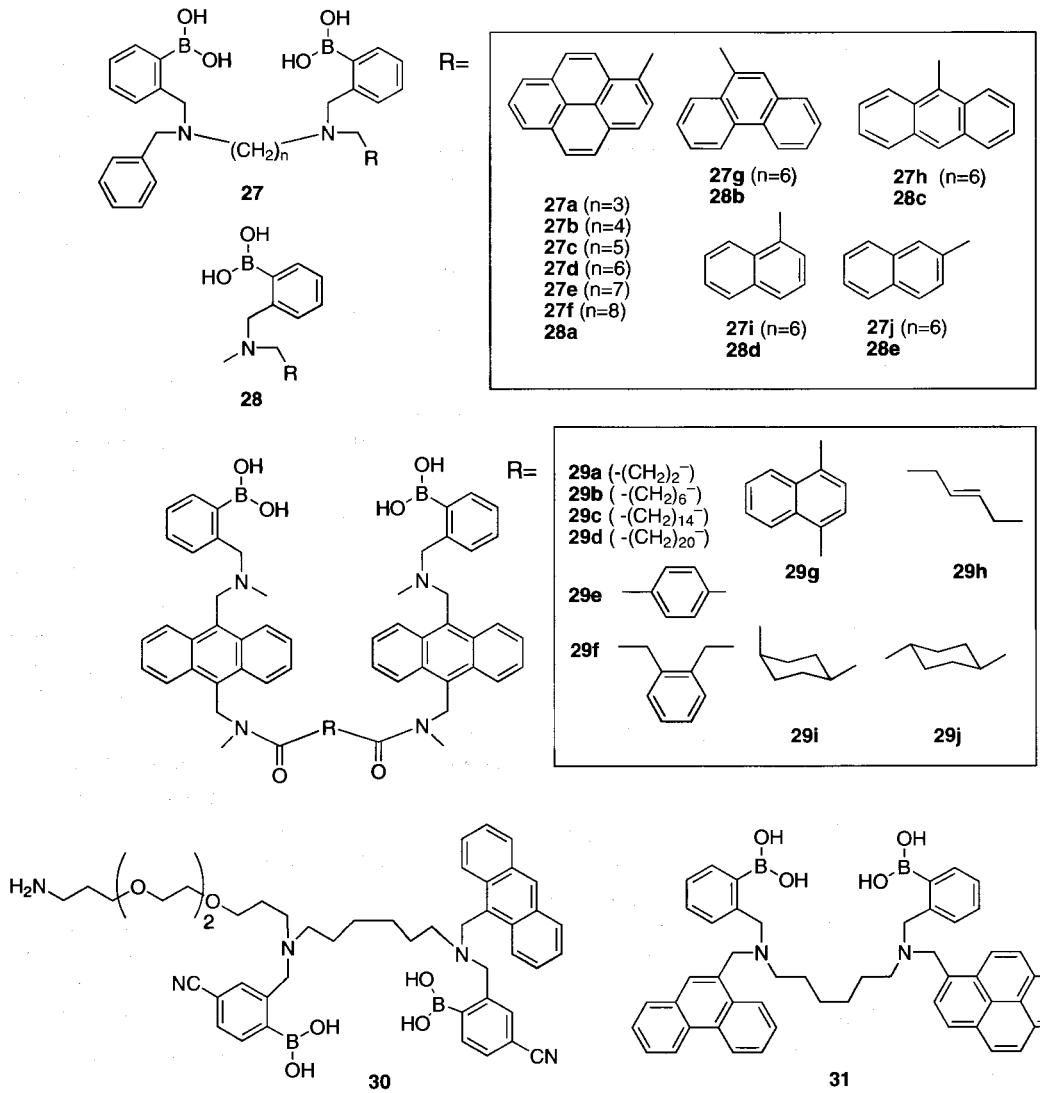


Figure 12.6 Modular boronic acid photoinduced electron transfer (PET) fluorescence sensors.

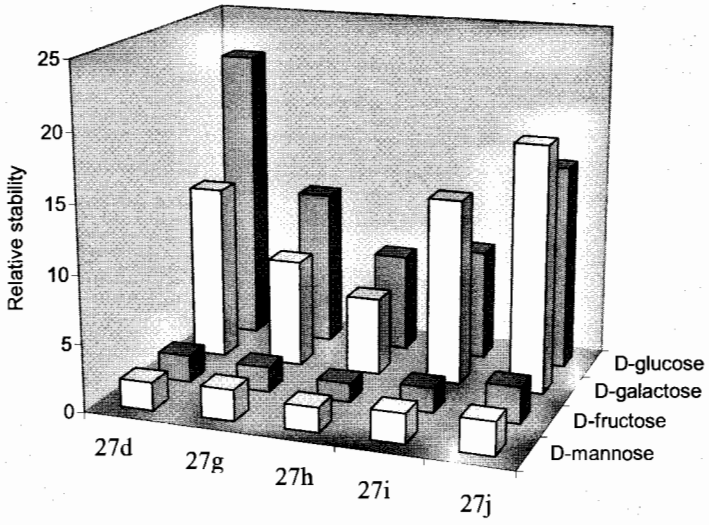


Figure 12.7 Relative stability of **27d, g–j** compared to **28a–e** with saccharides.

D-melibiose 339 M^{-1}, while the monoboronic acid **28a** has a binding constant of 96 M^{-1} in 52.1 wt% methanol–water at pH 8.21 (phosphate buffer). The selectivity of **27a–f** for D-melibiose mirrors that for D-glucose, indicating that these diboronic acid sensors form stable 1:1 cyclic structures with the furanose segment of D-melibiose [84]. These observations and those of Hall with polysaccharides complement the observations made by Norrild for monosaccharides [13, 14, 85].

With compound **31** James and co-workers have applied the same modular approach to prepare a saccharide sensing system using fluorescence energy transfer. Fluorescence energy transfer is the transfer of excited-state energy from a donor to an acceptor. The idea behind this system was to investigate the efficiency of energy transfer (ET) from phenanthrene to pyrene as a function of saccharide binding [86].

Sensor **31** is particularly interesting in that differences between the observed fluorescence enhancements obtained when excited at phenanthrene (299 nm) and pyrene (342 nm) can be correlated with the molecular structure of the saccharide-sensor complex. Fluorescence enhancement of sensor **31** with D-glucose is 3.9 times greater when excited at 299 nm and 2.4 times greater when excited at 342 nm. Whereas, with D-fructose the enhancement was 1.9 times greater when excited at 299 nm and 3.2 times greater when excited at 342 nm. These results indicate that energy transfer from phenanthrene (donor) to pyrene (acceptor) in a rigid 1:1 cyclic D-glucose complex is more efficient than in a flexible 2:1 acyclic D-fructose complex. The more efficient energy transfer leads to an enhanced fluorescence response to D-glucose. Observed K_{app} for **31** when excited at 299 and 342 nm were 76 and 125 M^{-1} for D-fructose, 74 and 81 M^{-1} for D-galactose and 142 and 108 M^{-1} for D-glucose in 52.1 wt% methanol–water at pH 8.21 (phosphate buffer).

The boronic acid PET system has also been used in combination with other binding sites. James and co-workers have explored the D-glucosamine selective fluorescent systems **32a,b** based on a boronic acid and aza crown ether [87, 88] (Figure 12.8). Sensors **32a,b** consist of monoaza-18-crown-6 ether or monoaza-15-crown-5 as a binding site for the ammonium terminal of D-glucosamine hydrochloride, while a boronic acid serves as a binding site for the diol part of D-glucosamine hydrochloride. The nitrogen of the azacrown ether unit can participate in PET with the anthracene fluorophore; ammonium ion binding can then cause fluorescence recovery. This recovery is due to hydrogen bonding from the ammonium ion to the nitrogen of the azacrown ether. The strength of this hydrogen-bonding interaction modulates the PET from the amine to anthracene. As explained above, the boronic acid unit can also participate in PET with the anthracene fluorophore and diol binding can also cause fluorescence recovery. The anthracene unit serves as a rigid spacer between the two-receptor units, with the appropriate spacing for the D-glucose guest. This system behaves like an AND logic gate [56, 89], in that fluorescence recovery is only observed when two chemical inputs are supplied, for this system the two chemical inputs are an ammonium cation and a diol group. Observed K_{app} for **32a,b** were 18, 17 M^{-1} for D-glucosamine in 33.2 wt% ethanol–water at pH 7.18 (triethanolamine buffer).

Takeuchi and Yamamoto have developed a D-glucuronic acid selective fluorescent system (**33**) based on a boronic acid and metal chelate [90, 91]. The behavior of the system has been analyzed with and without Zn(II). Fluorescence measurements indicate that binding with common monosaccharides (D-fructose, D-glucose and D-galactose) are not affected by incorporation of a Zn(II), whereas binding with uronic (D-glucuronic and D-galacturonic) acids and sialic (*N*-acetylneuraminic) acid are

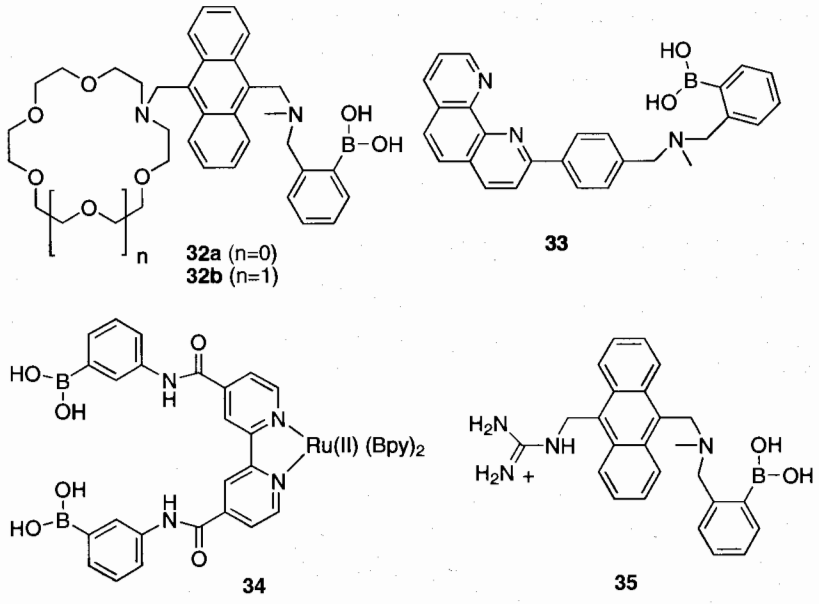


Figure 12.8 Ditopic fluorescence sensors.

greatly enhanced. K_{app} for **33** with and without Zn(II), respectively, were 250 and 316 M^{-1} for D-fructose, 1260 and 80 M^{-1} for D-galacturonic acid and 2510 M^{-1}, and no fluorescence change observed for D-glucuronic acid in 2:1 (v/v) methanol–water at pH 8.0 (MOPS buffer).

Deetz and Smith have prepared a heteroditopic ruthenium(II) bipyridyl receptor with both saccharide and phosphate binding sites **34** [92]. The receptor displays enhanced affinity for phosphorylated saccharides over normal saccharides. The system is also positively allosteric for saccharides in the presence of phosphate – the association constants increase by two orders of magnitude when titrations with saccharide are conducted in sodium phosphate buffer. Observed K_{app} for **34** were 32 M^{-1} for D-fructose, 1580 M^{-1} for D-fructose in 10 mM phosphate buffer and 1260 M^{-1} for D-fructose-6-phosphate in water at pH 7.3.

A D-glucarate system consisting of boronic acid and guanidinium receptor units has recently been reported by Wang [93]. K_{app} found for **35** were 62 M^{-1} for D-glucose, 46 M^{-1} D-glucuronic acid and 5142 M^{-1} for D-glucarate in 1:1 (v/v) methanol–water at pH 7.4.

12.2.3
Other Fluorescent Sensors

Wang has recently reported that 8-quinoline boronic acid (**36b**) responds to the binding of D-fructose with over 40-fold increases in fluorescence intensity, while D-glucose only produced a 3-fold fluorescence increase [94]. The authors ascribe the fluorescence changes to environmental factors and not to a change in the hybridization of the boron. K_{app} found for **36** (Figure 12.9) were 108 M^{-1} for D-fructose and 7.5 M^{-1} for D-galactose in water at pH 7.4 (phosphate buffer).

Heagy and Lakowicz have been investigating *N*-phenylboronic acid derivatives of 1,8-naphthalimide (**37a,b**, Figure 12.9) – with these systems the fluorescence is substantially quenched (ca. 5-fold) on saccharide binding [95, 96]. The fluorescence

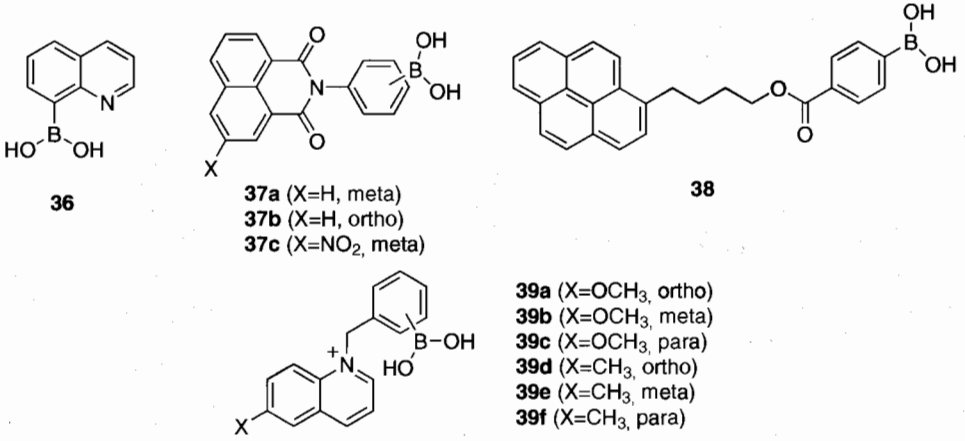


Figure 12.9 Monoboronic acid fluorescent sensors.

change has been ascribed to PET from the boronate to the naphthalimide fluorophore. Nitro derivative **37c** was particularly interesting because it displayed dual fluorescence and was particularly sensitive for D-glucose [97]. Observed K_{app} for **37a**, **b** and c were 769, 625 and 476 M^{-1} for D-fructose and 21.7, 17.5 and 38.5 M^{-1} for D-glucose in water at pH 7.5, 7.5 and 8.0, respectively (phosphate buffer).

Hayashita and Teramae have prepared an interesting fluorescent ensemble that consists of compound **38** and β-cyclodextrin [98]. The system displays fluorescence enhancement on saccharide binding and, as expected for a monoboronic acid, the highest binding was observed with D-fructose. Observed K_{app} for **38** were 2515 M^{-1} for D-fructose and 79 M^{-1} for D-glucose in 2% (v/v) DMSO-water at pH 7.5.

Lakowicz and Geddes have explored the use of several quaternized quinolium boronic acids (**39a–f**) for D-glucose monitoring within contact lenses [99].

Diboronic acids can bind monosaccharides selectively, where the 1:1 binding creates a rigid molecular complex [100–105]. This rigidification effect can also be utilized in designing fluorescent sensors for disaccharides. Sandanayake has investigated the binding of diboronic acid **40** (Figure 12.10) with disaccharides in basic aqueous media [106]. Excited stilbene is quenched by radiationless decay via rotation of the ethylene double bond. Obstruction of this rotation leads to increased fluorescence [107]. Rigidification of **40** by disaccharide binding increases the stilbene fluorescence. In particular, the disaccharide D-melibiose shows higher selectivity for **40** than other common disaccharides.

Takeuchi and co-workers have used molecular rigidification of cyanine diboronic acid **41** (Figure 12.10) to generate a fluorescence increase with added saccharides [108]. Observed K_{app} for **41** were 130 000 M^{-1} for D-fructose and 1400 M^{-1} for D-glu-

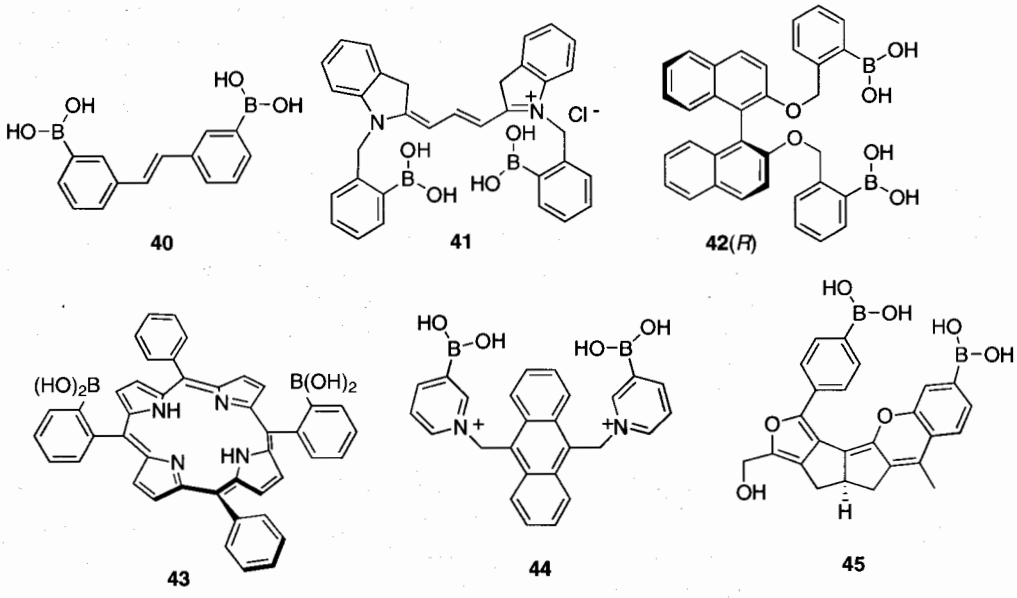


Figure 12.10 Diboronic acid fluorescent sensors.

cose in 1:1 (v/v) methanol–water at pH 10.0 (carbonate buffer). Rigidification has also been used with a diboronic acid appended binaphthyl, **42**(*R*), to develop a chirally discriminating system [109]. K_{app} for **42**(*R*) were 8600 M^{-1} for D-fructose, 14 400 M^{-1} for L-fructose, 2100 M^{-1} for D-glucose and 1900 M^{-1} for L-glucose in 1% (v/v) methanol–water at pH 10.8 (carbonate buffer).

Kijima et al. have developed a D-lactulose selective system (**43**) based on a diboronic acid porphyrin [110]. The spatial disposition of the two boronic acids in **43** produces the perfect 'cleft' for the disaccharide D-lactulose. K_{app} found for **43** was 560 M^{-1} for D-lactulose in methanol. Other disaccharides produced no spectral changes.

Norrild has developed the interesting diboronic acid system **44** [85]. This system works by reducing the quenching ability of the pyridine groups of **44** on saccharide binding. The structure of the complex was determined to be to a 1,2:3,5 bound α-D-glucofuranose. Evidence for the furanose structure was obtained from ^{1}H and ^{13}C NMR data, with emphasis on the information from $^{1}J_{C-C}$ coupling constants. The K_{app} observed for **44** was 2500 M^{-1} for D-glucose in water at pH 7.4 (phosphate buffer). D-Fructose and D-galactose were bound much more weakly than D-glucose, and the binding constants could not be determined using a simple 1:1 binding model.

All the systems described above for the selective binding of D-glucose have been designed using the approximate positioning of two boronic acid units. Many of these systems bind D-glucose strongly and selectively. In systems where the structure of the D-glucose complex has been determined the furanose rather than pyranose form of D-glucose is favored. Consequently, it was suggested that binding of the more abundant α-pyranose form of D-glucose by boronic acids should not be considered in the future design of boronic acid based sensors for aqueous systems [85].

Drueckhammer, however, has purposely set out to design a system selective for the pyranose form of D-glucose from first principles, using computational methods to define the exact placing of two boronic acid groups. The approach resulted in the design and synthesis of compound **45**, which shows very high binding towards D-glucose [111]. Compound **45** exhibited a 400-fold affinity for D-glucose over any of the other saccharides (D-galactose, D-mannose and D-fructose). ^{1}H NMR was used to confirm that the bound D-glucose was captured in the pyranose and not furanose form. The K_{app} found for **45** were 4000 M^{-1} for D-glucose and 100 M^{-1} for D-galactose in 30% methanol–water at pH 7.5 (phosphate buffer). With D-fructose the fluorescence response was too small for an accurate determination of the stability constant.

In a novel approach Hamachi coupled a natural receptor protein (Concanavalin A – ConA) with a fluorescent boronic acid PET system to prepare a semi-synthetic biosensor (**46**, Figure 12.11) [112]. The system illustrates how both synthetic and natural systems can be combined to generate biosensors with enhanced selectivity towards specific oligosaccharides. Observed K_{app} for **46** were 708 M^{-1} for D-fructose and 151 000 M^{-1} for D-palatinose in water at pH 7.5 (HEPES buffer).

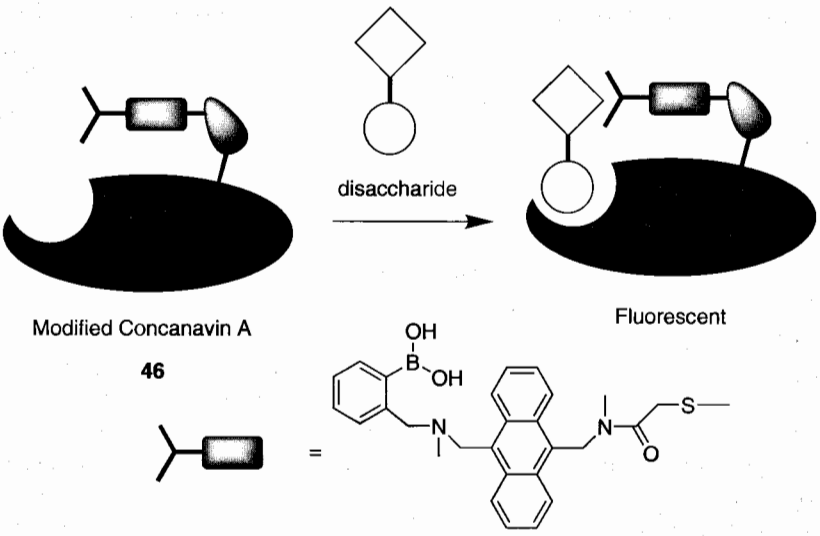


Figure 12.11 Semi-synthetic boronic acid fluorescent sensor.

12.3
Colorimetric Sensors

Colorimetric sensors for saccharides are of particular interest in a practical sense. If a system with a large color change can be developed it could be incorporated into a diagnostic test paper for D-glucose, similar to universal indicator paper for pH. Such a system would make it possible to measure D-glucose concentrations without the need of specialist instrumentation. This would be of particular benefit to diabetics in developing countries.

A fairly recent development has been the study of the effect of saccharides on the color of dyes containing boronic acid functionality. Boronic acid azo dyes have long been known, having been used for investigations in the treatment of cancer by a technique called boron neutron capture therapy (BNCT) [113, 114]. It was not until the 1990s that related dyes and their interaction with saccharides were studied. Russell has synthesized a boronic acid azo dye from *m*-aminophenylboronic acid, which was found to be sensitive to a selection of saccharides [115]. The usefulness of the dye as a D-glucose-monitoring agent in fermentation processes was proven by tests in beef-broth solution (used in the growth of bacteria) containing various proteins, lipids and salts. Nagasaki observed that chromophores containing boronic acid moieties (**47** and **48**, Figure 12.12) (which aggregate in water) changed color and de-aggregated upon complexation with saccharides [116]. This was rationalized by the boronic acid–saccharide complexation increasing the hydrophilicity of the bound species.

Takeuchi has prepared boronic acid dye **49** (Figure 12.12), which undergoes an absorption spectral change on addition of nucleosides [117]. The boronic acid binds with

the ribose, and the dimethylaminophenylazo moiety can stack with the adenine of the nucleoside.

Internal charge transfer (ICT) sensor **50** (Figure 12.12), prepared by Sandanayake, employs an intramolecular interaction between the tertiary amine and the boronic acid group to promote color changes on addition of saccharides [118]. The electron-rich amine creates a basic environment around the electron-deficient boron center, which has the effect of inducing the boronic acid–saccharide interaction and reducing the working pH of the sensor. Electronic changes associated with this decrease in the pK_a of the boronic acid moiety on saccharide complexation are transmitted to the neighboring amine. This creates a spectral change in the connected ICT chromophore, which can be detected as a change in color. The pK_a related to the boron–nitrogen interaction of **50** shifts on the addition of saccharides. The largest pK_a shift was found for D-fructose ($\Delta pK_a = 3.31$) and the smallest for simple diols such as ethylene glycol ($\Delta pK_a \approx 0$). The observed stability constant (K_{app}) for **50** was 138 M^{-1} for D-fructose in water at pH 7.6. The stability constant with D-glucose was not determined due to small spectral changes.

Shinmori et al. have synthesized a diboronic acid saccharide receptor bearing a photoresponsive azobenzene group, **51** that was used as a light-gated saccharide sensor [119]. When the azobenzene unit is switched by photoirradiation, from the more stable trans-conformation to the thermodynamically unfavorable cis-isomer, it shows high D-glucose and D-allose selectivity. The formation of cyclic 1:1 complexes between saccharide and the dye in its cis-geometry explains the selectivity order.

Koumoto and Shinkai demonstrated that azobenzene derivatives bearing one or two aminomethylphenylboronic acid groups **52** and **53** can be used for practical colorimetric saccharide sensing in 'neutral' aqueous media [120]. Observed K_{app} for **53** were 433 M^{-1} for D-fructose and 13.0 M^{-1} for D-glucose in 1:1 (v/v) methanol–water at pH 7.5 (phosphate buffer).

Koumoto has cleverly used the boronic acid–amine interaction for the molecular design of an intermolecular sensing system for saccharides [121]. 3-Nitrophenylboronic acid interacts with the pyridine nitrogen of 4-(4-dimethylaminophenylazo)-pyridine (**54**) in methanol and changes from yellow to orange. Added saccharides form complexes with the boronic acid and enhance the acidity of the boronic acid group. As a result the boron–nitrogen interaction becomes stronger and the intensified intramolecular charge-transfer band turns the solution red.

James and co-workers recently prepared diazo dye system **55a**, which shows a large visible change from purple to red on saccharide binding [122, 123]. With azo dye **55a** the wavelength maximum shifts by ca. 55 nm to a shorter wavelength upon saccharide complexation. K_{app} for **55a** were 2550 M^{-1} for D-fructose and 123 M^{-1} D-glucose in 52.1 wt% methanol–water at pH 11.32 (carbonate buffer).

With dye molecule **50** it was proposed that at intermediate pH a boron–nitrogen interaction exists, whereas at high and low pH this bond is broken. What makes the equilibria of dye molecule **55a** more interesting is the presence of the *anilinic hydrogen*, which can give rise to different species at high pH.

In the absence of saccharide, at pH 11.32, **55a** is purple, and in the presence of saccharide the color is red. In the presence of saccharide the B–N interaction becomes

stronger. The increased B–N interaction causes the N–H proton to become more acidic. Therefore at pH 11.32, the saccharide–boronate complex dehydrates (loss of H^+ from aniline and OH^- from boronate) to produce a red species with a covalent B–N bond.

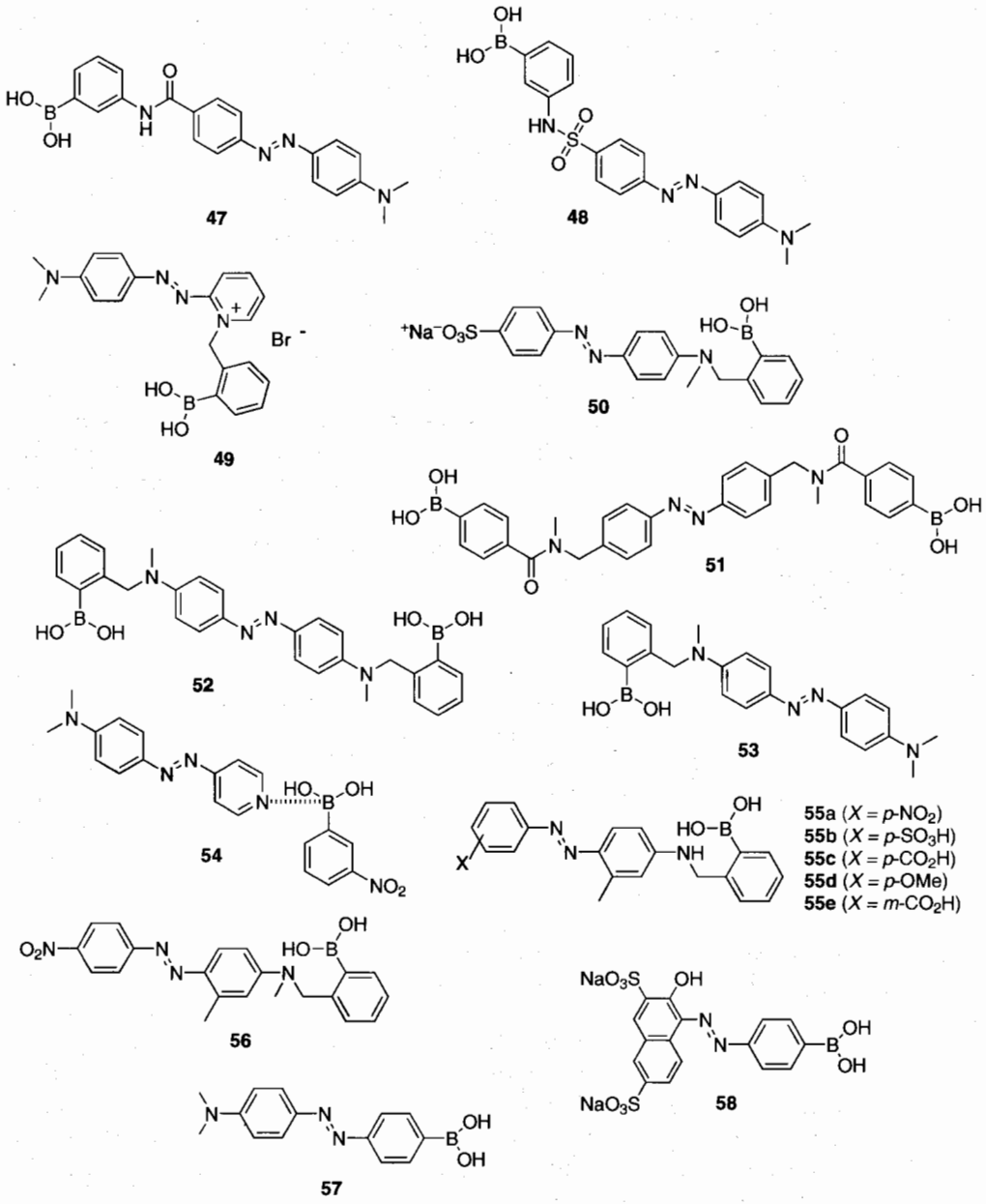
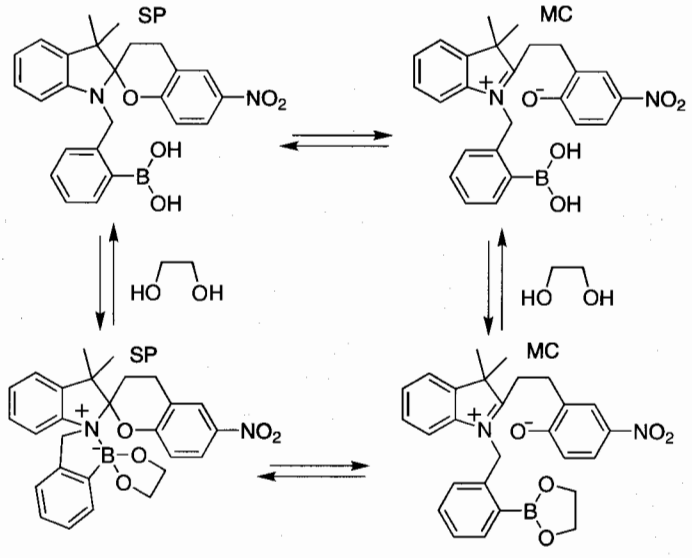


Figure 12.12 Azo-dye colorimetric sensors.

These equilibrium species explain why dye molecule **50** did not give a visible spectral shift on saccharide binding. With **50** there is no possibility of dehydration, so a strong boron–nitrogen bond cannot be formed; hence no spectral shift is observed. This hypothesis has been confirmed by evaluating **56**, which does not have an anilinic hydrogen. No color change was observed for **56** on addition of saccharides at pH 11.32 [123]. James and co-workers have also carried out a detailed investigation on a series of azo dyes with both electron-donating and -withdrawing groups (**55a–e**) and determined that a strong electron-withdrawing group is required to produce a color change [123].

Dicesare and Lakowicz have also prepared boronic acid azo dye molecules **57** and **58** in which direct conjugation with the boron centre is possible. In particular, azo dye **58** produces a visible color change from yellow to orange at pH 7 [124]. K_{app} for **58** were 158 M^{-1} for D-fructose and 2.7 M^{-1} for D-glucose in water at pH 7.0 (phosphate buffer).

Shinmori has shown that a boronic acid appended spirobenzopyran (**59**, Figure 12.13 below) undergo changes in the absorption spectra on the addition of saccharides [125]. The added saccharides change the position of the merocyanine (MC) to spiropyran (SP) equilibrium and hence change the color of the system. With added saccharide the SP structure is favored due to a stronger B–N interaction in the saccharide complex (Scheme 12.5).



Scheme 12.5 Effect of saccharides on the spiropyran versus merocyanine equilibrium.

Yamamoto and co-workers have used the change in redox potential of **60** to modulate the color of **61** (Figure 12.13). When saccharides bind with **60** the pK_a of the boronic acid is lowered, which in turn alters the redox potential of the ferrocene moi-

ety. Dye molecule **61** was chosen since its redox potential was such that reduction by the ferrocene unit becomes facile as the redox potential of the ferrocene lowers on addition of saccharides [126].

Mizuno et al. have investigated the use of chiral salen cobalt(II) complexes **62** (*R*) and **63** (*R*) (Figure 12.13) [127]. Spectroscopic changes in the metal complexes were used to monitor the formation of the saccharide complexes. Chiral discrimination was observed with **62** (*R*), which showed two-fold selectivity for L-allose over D-allose. Mizuno has also used a prochiral salen cobalt(II) complex; the binding and chirality was monitored using circular dichroism (CD) spectroscopy [128]. Observed stability constants (K_{app}) for **62** (*R*) were 2760 M^{-1} for D-fructose, 2700 for L-fructose, 240 M^{-1} for D-glucose, 250 M^{-1} for L-glucose, 360 M^{-1} for D-allose and 780 M^{-1} for L-allose in **1:1** (v/v) methanol–water at pH 9.5 (carbonate buffer). K_{app} for **63** (*R*) were 170 M^{-1} for D-glucose, 210 M^{-1} for L-glucose, 200 M^{-1} for D-allose and 320 M^{-1} for L-allose in 1:1 (v/v) methanol–water at pH 9.5 (carbonate buffer).

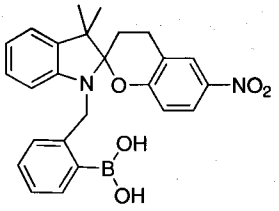
Yam and Kai [129] and a detailed reinvestigation by Mizuno and co-workers [130] have explored the sensing properties of boronic acid appended rhenium (I) complex **64**. This system and **62** and **63** illustrate how metal chelation can be used to extend the working wavelength of a sensor.

Strongin and co-workers have prepared a tetraboronic acid resorcinarene system **65** for the visual sensing of saccharides [131]. Characteristic color changes were observed for specific carbohydrates, D-glucose phosphates and amino sugars on gentle heating in DMSO. Further work by Strongin with another resorcinol derivative, **66**, has shown that oxygen promotes the color changes and that the resorcinol hydroxyl groups play a key role in the color formation of the solutions [132]. The mechanism of color change points to xanthenes as in situ chromophores formed by heating resorcinols in DMSO. Non-boronic acid receptors also produce colored solutions but to a lesser extent. In these cases the color is due to hydrogen bonding between aldonic acids (heating sugars in DMSO produces aldonic acid derivatives) and the hydroxyls of the in situ xanthene chromophore [133].

Results obtained with **55a–e** led James and co-workers to prepare the strongly electron-withdrawing tricyanovinyl dye **67**. The pK_a of **67** (7.81) was much less than that of **55a** (10.2), resulting in a visible color change on addition of saccharides at a much lower pH (8.21) [134]. Observed stability K_{app} for **67** were 170 M^{-1} for D-fructose and 8.3 M^{-1} for D-glucose in 52.1 wt% methanol–water at pH 8.21 (phosphate buffer).

Sato et al. have prepared stilbazolium boronic acids **68** and **69** and demonstrated the suitability of this unit for the optical sensing of saccharides [135]. Observed K_{app} for **68** and **69** were 220 and 280 M^{-1} for D-fructose and 4 and 6 M^{-1} D-glucose in 4% acetonitrile–water at pH 7.0 (phosphate buffer).

Wang has prepared nitrophenol boronic acids **70** and **71**, which show large UV shifts on addition of saccharides. These shifts have been attributed to a change in the balance of the phenolate to boronate equilibria in the presence of saccharides [136]. K_{app} for **70** and **71** were 245 and 13.5 M^{-1} for D-fructose and 8.0 and 1.2 M^{-1} for D-glucose in 4% (v/v) methanol–water at pH 7.4 (phosphate buffer).



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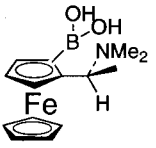

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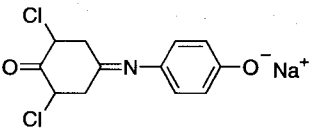

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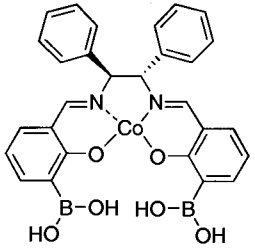
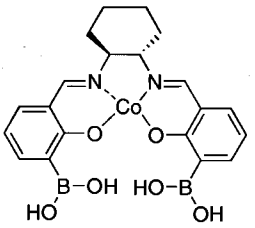
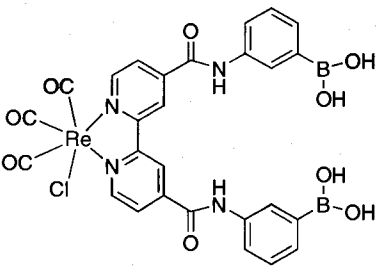


62 (*R*)



63 (*R*)



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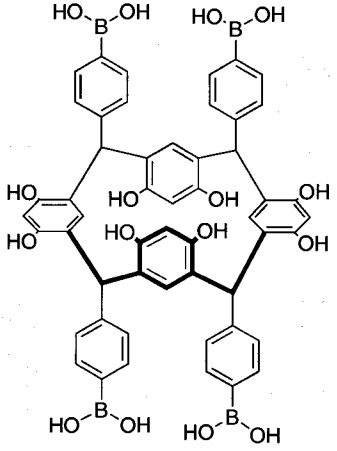

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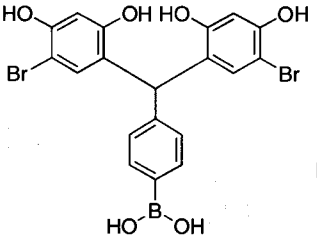

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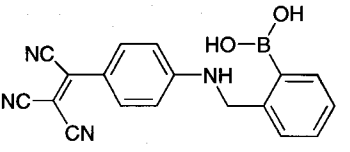

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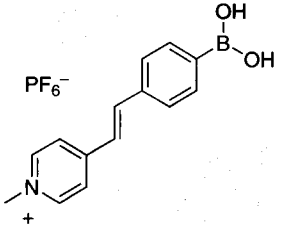

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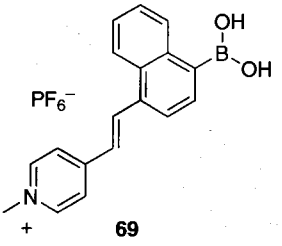

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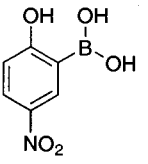

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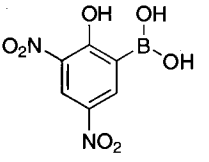


71

Figure 12.13 Non-azo-dye colorimetric sensors.

12.4
Electrochemical Sensors

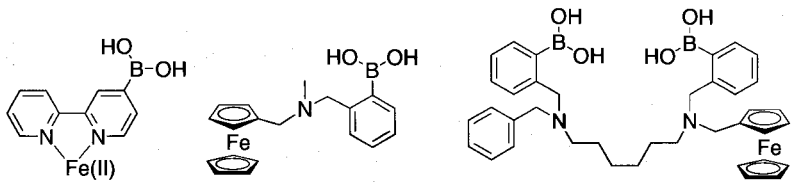
Electrochemical detection of saccharides by enzymatic decomposition of saccharides is the basis of most current commercial D-glucose biosensors [137]. The development of boronic acid based electro-active saccharide receptors for D-glucose is also possible. However, the main value of the boronic acid based synthetic systems is that they could provide selectivity for a range of saccharides other than D-glucose.

Chiral ferroceneboronic acid derivatives (– or +)-**60** have been synthesized and tested for chiral electrochemical detection of monosaccharides [138]. The best discrimination was observed for L-sorbitol and L-iditol at pH 7.0 in 0.1 mol dm^{-3} phosphate buffer solution.

Moore and Wayner have explored the redox switching of carbohydrate binding with commercial ferrocene boronic acid [139]. From their detailed investigations they have determined that binding constants of saccharides with the ferrocenium form are about two orders of magnitude greater than for the ferrocene form. The increased stability is ascribed to the lower pK_a of the ferrocenium (5.8) than ferrocene (10.8) boronic acid.

Fabre and co-workers have investigated the electrochemical sensing properties of boronic acid substituted bipyridine iron(II) complex **72** [140]. On addition of 10 mM D-fructose the oxidation peak was shifted by 50 mV towards more positive values.

James and co-workers have prepared a ferrocene monoboronic acid (**73**) and diboronic acid (**74**) as electrochemical saccharide sensors (Figure 12.14) [141]. Monoboronic acid system **73** has also been prepared and proposed as an electrochemical sensor for saccharides by Norrild [142]. Electrochemical saccharide sensor **74** contains two boronic acid units (saccharide selectivity), one ferrocene unit (electrochemical read out) and a hexamethylene linker unit (for D-glucose selectivity). Electrochemical sensor **74** displays enhanced D-glucose (40×) and D-galactose (17×) selectivity compared with the monoboronic acid **73**.

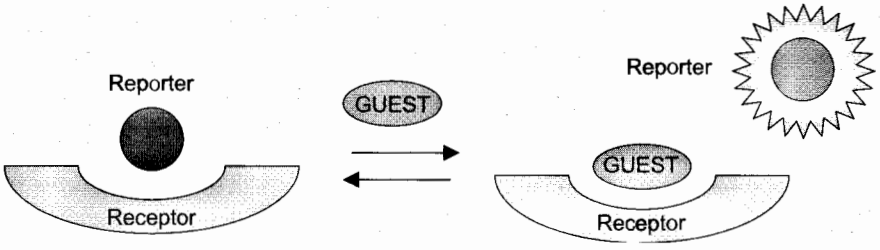


72 **73** **74**

Figure 12.14 Electrochemical sensors.

12.5
Assay Systems

So far we have discussed the development of integrated molecular sensors using boronic acids. The systems contain a receptor and reporter (fluorophore or chromophore) as part of a discrete molecular unit. However, another approach towards boronic acid based sensors is also possible, where the receptor and a reporter unit are separate, as in a competitive assay. A competitive assay requires that the receptor and reporter (typically a commercial dye) associate under the measurement conditions. The receptor–reporter complex is then selectively dissociated by the addition of the appropriate guests. When the reporter dissociates from the receptor, a measurable response is produced (Scheme 12.6).



Scheme 12.6 Cartoon depicting the function of an assay system.

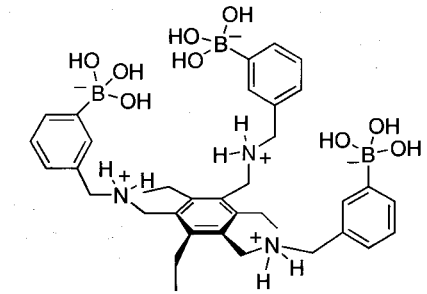
The competitive assay approach to novel chemosensors has been pioneered by Anslyn [143]. These competitive systems are particularly interesting because they reduce the synthetic complexity of the receptor.

Anslyn has recently reported two very elegant systems based on boronic acid receptors. Although the Anslyn systems involve a competitive colorimetric assay, there is no reason why the system cannot be extended to a fluorimetric assay through the choice of appropriate dye molecules. The first system is a receptor for D-glucose-6-phosphate (**75**) [144]; binding of D-glucose-6-phosphate is measured through the competitive displacement of 5-carboxyfluorescein. The second is a system where the binding of heparin and **76** (Figure 12.15) is monitored through displacement of pyrocatechol violet [145].

Arimori et al. have used compounds **77** and **78** with 1,5- or 2,6-anthraquinone disulfonates (ADS) in a competitive system for the fluorescence detection of D-fructose [146]. 1,5- or 2,6-ADS binds with **77** or **78** and quenches the fluorescence; addition of D-fructose causes decomplexation and fluorescence recovery.

Lakowicz and co-workers have also used competitive interactions between a ruthenium metal–ligand complex, a boronic acid derivative and D-glucose [147]. The metal–ligand complex forms a reversible complex with 2-tolylboronic acid or 2-methoxyphenyl boronic acid. Complexation is accompanied by a several-fold increase in the luminescent intensity of the ruthenium complex. Addition of D-glucose results in decreased luminescent intensity, which appears to be the result of decreased binding between the metal–ligand complex and the boronic acid. Ruthenium metal–lig-

and complexes are convenient for optical sensing because their long luminescent decay times allow lifetime-based sensing with simple instrumentation. However, with this system 40 mM D-glucose produces only an 11% change in intensity.



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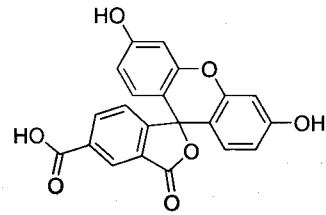
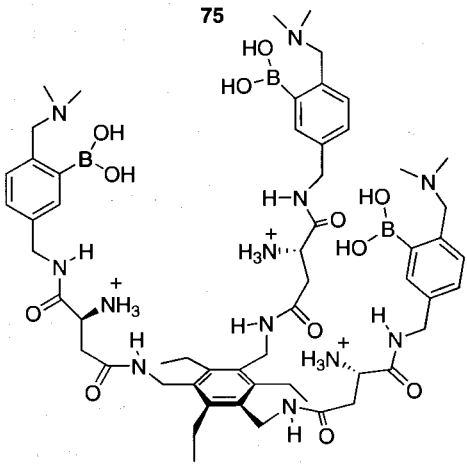


5-carboxyfluorescein



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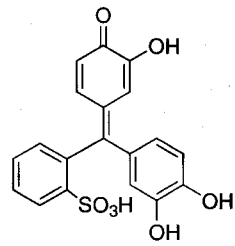
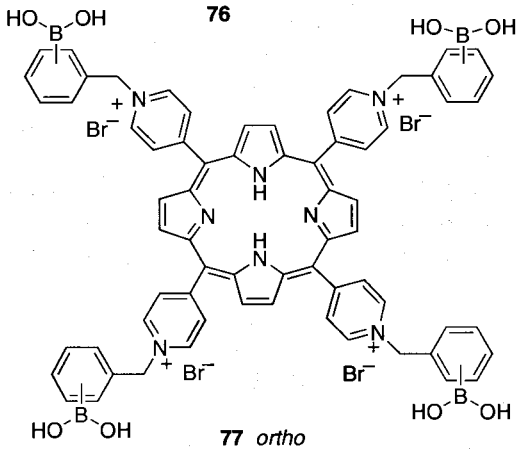
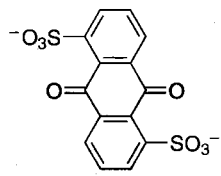


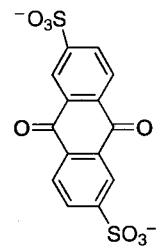
pyrocatechol violet



77 *ortho*
78 *meta*



1,5-ADS



2,6-ADS

Figure 12.15 Assay sensors.

An interesting multicomponent system has also been devised by Singaram, where quenching of a pyranine dye by bisboronic acid viologen units **79** and **80** is modulated by added saccharide [148, 149]. Compound **79** (Figure 12.16) binds well with D-fructose (K_{app} = 2600 M^{-1}) and weakly with D-glucose (K_{app} = 43 M^{-1}) in pH 7.4 phosphate buffer; however, the system only produces a 4% fluorescence recovery [149]. Compound **80** binds well with both D-fructose (K_{app} = 3300 M^{-1}) and D-glucose (K_{app} = 1800 M^{-1}) in pH 7.4 phosphate buffer. Together with the enhanced selectivity for D-glucose this system also produces a 45% fluorescence recovery on addition of saccharides [148].

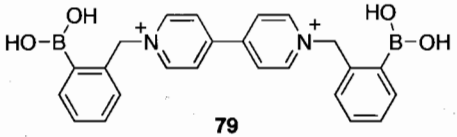
Lakowicz has also examined the quenching and recovery of a sulfonated poly(phenylene ethynylene) by a bisboronic acid viologen (**81**) on addition of saccharides [150]. The system is D-fructose selective and produces up to 70 fold fluorescence enhancement on addition of saccharides.

Wang has recently shown that alizarin red S and phenyl boronic acid (PBA) could be used in competitive assays for saccharides [151, 152]. The system is D-fructose selective, which is the expected selectivity for a monoboronic acid system [12]. It takes advantage of the known interaction of alizarin red S with boronic acids [153]. Observed stability constants (K_{app}) for the PBA alizarin red S assay were 160 M^{-1} for D-fructose and 4.6 M^{-1} for D-glucose in water at pH 7.4 (phosphate buffer).

James and co-workers have also used alizarin red S in the design of a D-glucose selective fluorescent assay. Receptor **82** was based on the successful fluorescent PET sensor **27d** [154]. Sensor **82** and alizarin red S show a six-fold enhancement over PBA for D-glucose. Sensor **82** can also be used at a concentration ten times lower than PBA. K_{app} for **82** were 140 M^{-1} for D-fructose and 66 M^{-1} for D-glucose in 52.1 wt% methanol–water at pH 8.21 (phosphate buffer).

Alizarin red S has also been used by Basu with several commercial monoboronic acids – 3-methoxycarbonyl-5-nitrophenyl boronic acid was much more efficient than PBA in competitive assays [155] and K_{app} for this boronic acid was 1350 M^{-1} for D-fructose in 2.5–3.8% (v/v) THF–water at pH 7.5 (PBS buffer).

From what has been described above, the fluorescent assay method seems to represent one of the best ways forward in the design of saccharide selective sensors. However, in a competitive assay all competition must be controlled so that the signal can be used to produce an analytical outcome. Therefore, presence of previously unrecognized interactions between boronic acids and buffer conjugate bases (phosphate, citrate and imidazole) [20] to create ternary complexes (boronate-X-saccharide) will need to be considered in future assay design.



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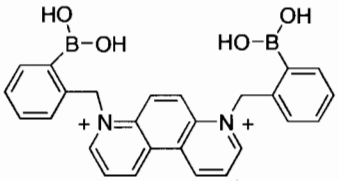

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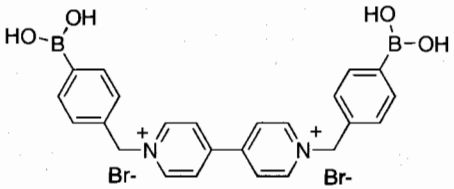

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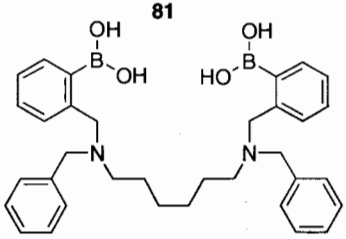
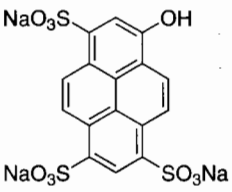
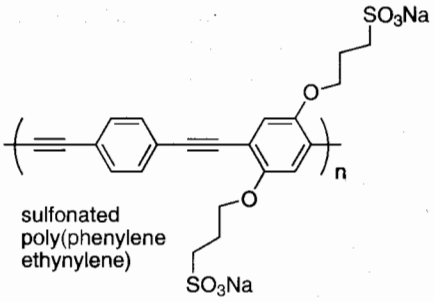


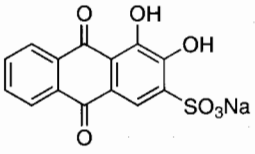
82



8-hydroxypyrene-1,3,6-trisulfonic acid



sulfonated poly(phenylene ethynylene)



Alizarin Red S

Figure 12.16 More assay sensors.

12.6 Polymer and Surface Bound Sensors

If practically useful sensors are to be developed from the boronic acid sensors described above, then they will need to be integrated into a device. One way to help achieve this goal is to incorporate the saccharide-selective interface into a polymer support.

Smith has prepared a grafted polymer containing a ribonucleoside 5′-triphosphate selective sensor. The polymers were prepared using poly(allylamine) (PAA) to which 10% of boronic acid monomer unit **83** (Figure 12.17) was grafted [156]. Also, a library

of potential sialic acid receptors was prepared [157]. In this case the polymers were prepared using PAA to which 2% of the boronic acid monomer unit **83** was grafted. The final polymers also contained various amounts of 4-hydroxybenzoic acid, 4-imidazolacetic acid, octanoic acid and/or succinic anhydride.

Nagasaki and Kimura have used polymers of poly(lysine) with boronic acids appended to the amine residue as saccharide receptors [158–160]. On saccharide complexation these polymers are converted from neutral sp^2 boron into anionic sp^3 hybridized boron. The anionic polymer thus formed interacts with added cyanine dye. Saccharide binding can then be 'read-out' by changes in the absorption and induced circular dichroism (ICD) spectra of the cyanine dye molecule.

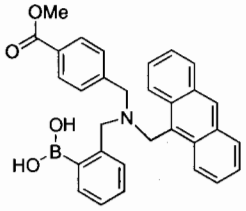
Wang has employed the template approach using monomer **84** to prepare a fluorescent polymer with enhanced selectivity towards D-fructose [161, 162]. Appleton has used a similar approach using monomer **85** to prepare a D-glucose selective polymer [77]. The Appleton polymer clearly shows the value of the imprinting technique. Here, the selectivity of the monomer for D-fructose over D-glucose has been reversed in the polymeric form.

James and co-workers have developed polymer sensors by grafting a solution based D-glucose selective receptor **27d** to a polymer support [78]. The major difference between the polymer-bound system **86** and solution-based system **27d** is the D-glucose selectivity, which drops for polymer **86** (whereas the selectivity with other saccharides is similar to those observed for compound **27d**). However, the polymeric system still has enhanced D-glucose selectivity (nine times) over the monoboronic acid model compound. The reduced binding of **86** for D-glucose has been attributed to the proximity of the receptor to the polymer backbone.

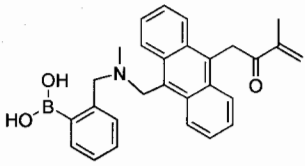
Kawanishi has also developed a membrane in which the PET-based D-glucose sensing system **19** has been immobilized to generate the polymer system **87**. The amide group was introduced not only as a linker to the membrane but also to shift the excitation and emission maxima to longer wavelengths. The fluorescent boronic unit has also been attached to the membrane through two linkers (via the two amino nitrogens). However, with two linkers the fluorescence response and affinity for D-glucose were reduced. These results indicate that single chain immobilization is superior to double chain immobilization. It was also confirmed that **87** can sense D-glucose in blood [163].

Singaram has made a significant breakthrough in the development of a continuous D-glucose monitoring system by incorporating his assay system, consisting of a pyranine dye and bisboronic acid viologen units, into a thin film hydrogel, **88** [164]. The system can detect D-glucose in the physiologically important range 2.5–20 mM and operates reversibly under physiological conditions, i.e., 37 °C, 0.1 μM ionic strength and pH 7.4.

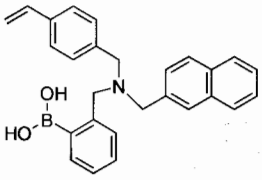
Asher has developed an attractive system using a crystalline colloidal array (CCA) incorporated into a polyacrylamide hydrogel and created a polymerized crystalline colloidal array (PCCA). Two systems have been developed, one is a polyacrylamide that has pendant boronic acid groups and works in low ionic strength solutions [165]. The other has pendant polyethylene glycol or **15**-crown-**5** and boronic acid groups and works in high ionic strength solutions [166]. The embedded CCA diffracts visible



83



84



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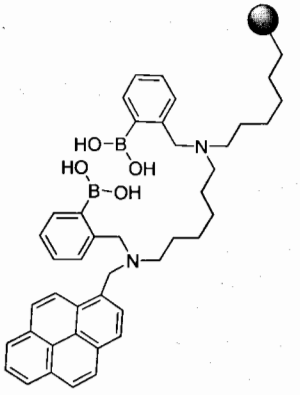
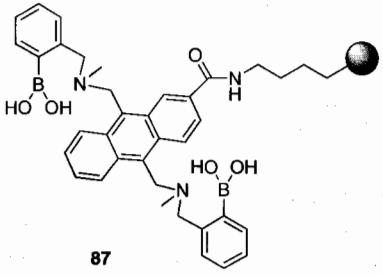
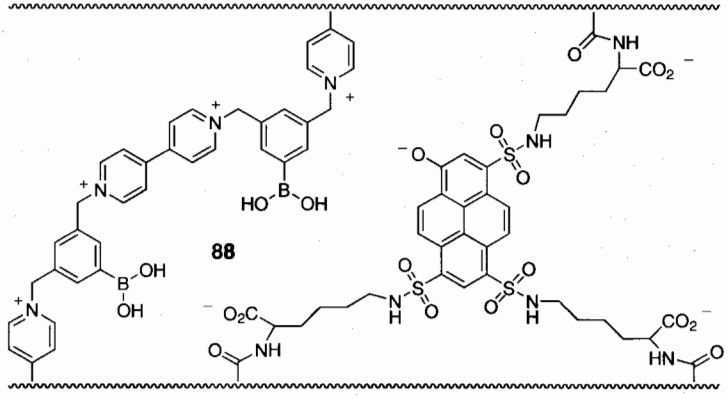


86



87



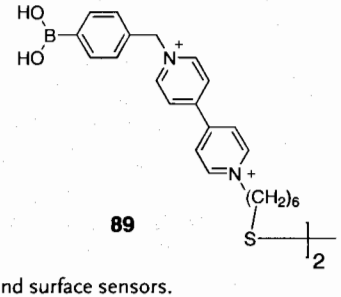


Figure 12.17 Polymer and surface sensors.

light, and the PCCA diffraction wavelength reports the hydrogel volume. The PCCA photonic crystal sensing material responds to D-glucose by swelling and red shifting the diffraction as the D-glucose concentration increases.

Wolfbeis has prepared a polyaniline with a near-infrared optical response to saccharides. The film was synthesized by copolymerization of aniline and 3-aminophenyl boronic acid. Addition of saccharides at pH 7.3 led to changes in absorption at 675 nm [167].

Nakashima has prepared a phenylboronic acid terminated redox active self-assembled monolayer on a gold electrode as an electrochemical sensor for saccharides. Self-assembled monolayers of **89**, a phenylboronic acid terminated viologen alkyl disulfide, function as a sensitive saccharide sensor in aqueous solution [168].

Freund has prepared polyaniline boronic acids by the electrochemical polymerization of 3-aminophenyl boronic acid [169, 170]. The electrochemical potential of the polymer is sensitive to changes in the pK_a of the polymer as a result of boronic acid–diol complex formation. Fabre has also used polyaniline boronic acids as a conductiomeric sensor for dopamine [171].

Several other polymers containing 3-aminophenylboronic acid [172] and vinylphenylboronic acid [173] groups have been evaluated as electrochemical saccharide sensors.

Boronic acids have been used in the development of surface plasmon resonance (SPR) [174, 175] quartz crystal microbalance (QCM) sensors [174, 176, 177], Faradaic impedance spectroscopy [177], ion-sensitive field effect transistors (ISFET) [178], and chemical exchange saturation transfer (CEST) contrast agents in magnetic resonance imaging (MRI) [179]. The swelling of phenylboronic acid polymers has also been used to control the release of insulin [180, 181].

12.7 Conclusions

"Our imagination is stretched to the utmost, not, as in fiction, to imagine things which are not really there, but just to comprehend those things which 'are' there."
Richard Feynman (1918–1988)

So what should be gleaned from this chapter or, put another way, what are the take home messages? Two main conclusions can be derived from the chemistry described (1) *A selective interface for saccharides requires at least two appropriately positioned boronic acid units.* The geometry and choice of the receptors used will be determined by the target saccharide and synthetic constraints. (2) *Signal read-out can be provided by an integrated fluorophore-receptor or fluorophore/receptor ensemble.* The choice of integrated or assay system depends on the application; integrated systems can be more difficult to synthesize while with ensembles obtaining an analytical output is non-trivial. For continuous monitoring an integrated sensor is probably the best choice, while an assay system could be cheaper and hence more suitable for use in disposable sensor kits.

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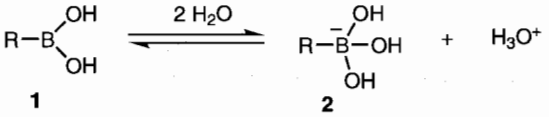
13
Biological and Medicinal Applications of Boronic Acids

Wenqian Yang, Xingming Gao, and Binghe Wang

13.1
Introduction

In the development of biological and pharmaceutical agents, biomimicry is an important principle. Since the organic world is based on carbon, an element that is similar but different from carbon should occupy a special place for biomimicry design. Such is the case for boron. Among the different oxidation states, boronic acid is the most useful for biological applications because of (1) its ready inter-convertibility between the sp^2 and sp^3 forms (Scheme 13.1), (2) its strong interaction with diol-containing compounds, (3) its Lewis acidity, and (4) its unique behavior upon neutron bombardment. Based on these unique properties, boronic acids have been used as enzyme inhibitors, sensors and lectin mimics that can be termed as boronolectins, boron neutron capture therapy agents, transmembrane transporters, in bioconjugations, and for protein immobilization.



Scheme 13.1 Conversion from a neutral and trigonal planar sp^2 boron into an anionic tetrahedral sp^3 boron.

In medicinal chemistry, the use of boronic acids as enzyme inhibitors largely reflects the usefulness of boron as a carbon analog in the binding process, but not in terms of reactions, which is the essence of a good enzyme inhibitor. One unique property of boronic acids is their strong Lewis acidity because of the boron open shell. Most arylboronic acids, for example, have an apparent pK_a in the range 4.5–8.8 [1, 2], depending on the aryl substitution [3, 4]. This means that, with the appropriate substitution, boronic acids would have the right property for ready conversion from a neutral, trigonal planar sp^2 boron (1) into an anionic tetrahedral sp^3 boron (2) (Scheme 13.1) under physiological conditions. Realizing that the process of cleaving

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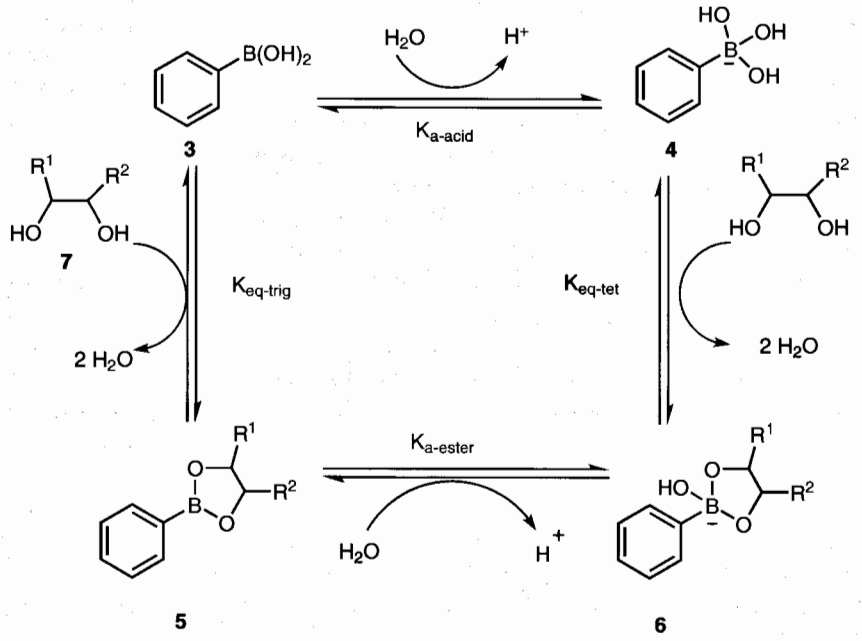
an amide or ester bond also requires the conversion of an sp^2 carbonyl carbon to a tetrahedral sp^3 carbon, it is easy to understand why boronic acid compounds would make good transition state analogs for the inhibition of hydrolytic enzymes. This is indeed the case. Some twenty years ago, simple alkyl or arylboronic acids were recognized as serine protease inhibitors [5–7]. Since then, many boronic acid compounds with an appropriate peptide sequences have been designed and synthesized for the development of more potent and selective inhibitors [8, 9]. Compared with aldehyde-based inhibitors of hydrolytic enzymes, the ready conversion of boronic acids into their anionic sp^3 form seems to make them better transition state analogs [10]. Boronic acids have been used for the development of enzyme inhibitors of peptidases/proteases, the proteasome, arginase, nitric oxide synthase (NOS), esterases, as well as transpeptidases. Although not the emphasis of this chapter, it needs to be noted that Matteson et al. has established a general synthetic route to chiral α-acetaminoalkylboronic acids with increased stability by stereoselective homologation of pinanediol boronic esters [10–12]. This enabled the synthesis of many potent boronic acid-based enzyme inhibitors. Thereafter, several variations of the general route have been developed and used for these synthesis of different kinds of enzyme inhibitors [13–17]. The development of the synthetic methodologies is discussed in detail in Chapter 8, and therefore will not be duplicated here.

The second type of applications of boronic acid compounds, described in Sections 13.4 and 13.5, relies on the known strong and reversible complexation between boronic acid and diol (1,2- or 1,3-)-containing compounds [3, 18]. Importantly, there are three ways to define the binding constants between a boronic acid and a diol (Schemes 13.2 and 13.3), using K_{trig}, K_{tet}, and K_{eq}. Wang and co-workers [3] have examined this issue and pointed out that the binding constants determined using the so-called pH depression method [18] are K_{tet}, not K_{eq}, which is the reason for some confusion and discrepancies in the literature [19–21]. By taking advantage of their strong, reversible interactions with diols, boronic acids have been used for the preparation of sensors for saccharide [22, 23], feed-back (glucose) controlled delivery systems for insulin [24], and boronolectins that recognize cell surface saccharide biomarkers [9, 25, 26]. The saccharide sensor part is addressed in Chapter 12, and therefore will not be discussed in this chapter unless it is directly related to biological applications other than simple sensing. The remaining two parts involving diol–boronic acid interactions will be discussed in detail in Sections 13.4 and 13.5.

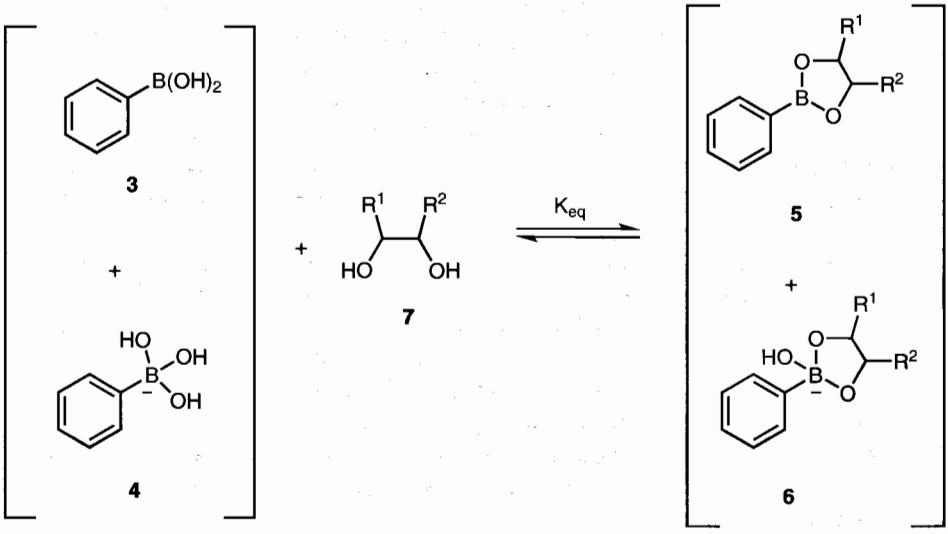
In addition to being developed as enzyme inhibitors and boronolectins, boron-based compounds (not limited to boronic acid compounds although that is the focus of this chapter) are also being studied for their utility as boron neutron capture therapy (BNCT) agents [27, 28]. Such applications are based on the unique property of boron-10, which emit α particles upon irradiation with neutron. Since α particles travel only a few mm they are ideal for localized radiation therapy. Therefore, targeted delivery of high concentrations of boron agents can be used for BNCT of certain tumors.

Because of the importance of boronic acids as potential pharmaceutical agents, we must ask whether they posses intrinsic and unusual toxicity and stability problems. The recent approval of bortezomib (Velcade), which is a boronic acid-based protea-

some inhibitor, by the US Food and Drug Administration for treatment of multiple myeloma [29] seems to provide at least a partial answer, i.e., there are no unique and intrinsic unacceptable toxicity and stability problems with boronic acid compounds [30, 31]. However, this is certainly not to say that all boronic acid compounds are de-



Scheme 13.2 Binding process between phenylboronic acid and a diol.



Scheme 13.3 Overall binding process between phenylboronic acid and a diol.

void of toxicity and stability problems. For example, even with clinically approved bortezomib toxicological studies in the rat and monkey have identified hematological, lymphoid, cardiac, renal, gastrointestinal, and neurological toxicities [30], although it is hard to imagine that all these toxicities are attributable to the intrinsic properties of the boronic acid moiety. Boronic acid compounds generally have sufficient stability to be used as pharmaceutical agents. For example, bortezomib has a plasma half-life of 9–15 h in human. Under laboratory conditions, degradation of the boronic acid moiety leads to deboronation via either hydrolysis or oxidation [32], with boric acid being the eventual product for the boron part. For example, degradation of bortezomib under acidic and basic conditions seems to be mediated by an initial oxidation, similar to that seen with peroxide oxidation [33]. The end product, boric acid, is not considered especially toxic to humans [34]. In a comparative toxicological study of borate, it has been estimated that daily consumption of about 3.3 g is required before male reproductive toxicity and developmental toxicity in human would become an issue [35]. Notably, boric acid is present in certain food such as nuts, fresh and dried fruits, and wine at fairly high concentrations, and normal boron intake has been estimated to be 1–7 mg per day [36], which is what the human population has to live with regardless of the intake of medications [36]. Furthermore, pregnancy has little or no effect on the renal clearance of boric acid in both rats and humans [37]. Overall, boronic acids are not expected to pose a unique set of intrinsic toxicity problems as pharmaceutical agents, although individual toxicities need to be evaluated, just as with any other new pharmaceutical agents.

This chapter discusses the application of boronic acids as potential enzyme inhibitors, artificial lectins (boronolectins), feed-back controlled drug delivery materials, boron neutron capture therapy agents, and other biologically active agents. The discussion focuses on the underlying chemical principles important for the various applications using selected examples. It does not strive to be comprehensive in terms of covering all the literature reports in this area, for which one can consult various reviews already [9, 38–40]. Boronic acids have also been used for the transport of various compounds such as ribonucleosides [41], amino acids [42], catecholamine [43], and saccharides across membranes [44–47]. However, such applications are more aimed for purification and separation and, therefore, will not be addressed in detail in this chapter.

13.2
Boronic Acid Compounds as Enzyme Inhibitors

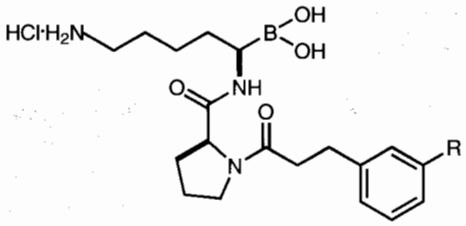
Various boronic acid compounds have been widely studied for their inhibition of different enzymes. The following discussion is divided based on the target enzymes and/or kind of approach used for the design of boronic acid-based enzyme inhibitors. At the end of the section, many examples are summarized in a table format for reference.

13.2.1
Protease Inhibitors that Bind to One Side of the Active Site

Proteases, which catalyze the hydrolysis of the amide bond of a protein or peptide, were among the very first enzymes to be targeted using boronic acid compounds [5, 6]. This is for good reasons. First, proteases play very important roles in numerous biological and pathological processes [48]. Second, a well-recognized approach of designing protease inhibitors is the design and synthesis of transition state analogs. Typically, this is done with the design of compounds that have a tetrahedral configuration, which resembles the tetrahedral intermediate during the cleavage process at the scissile bond position. As discussed earlier, most boronic acids can exist in both the neutral trigonal form and the anionic tetrahedral form under physiological conditions (Scheme 13.1). This means that properly designed boronic acid compounds can resemble both the substrate with an intact amide bond, which allows for its easy entry into the enzyme active site, and the tetrahedral intermediate during hydrolysis, which allows for the tight binding to the enzyme. Therefore, boronic acids are almost ideal candidates for the design of transition state analogs for proteases. Indeed, there are numerous examples of using boronic acids as protease inhibitors. In all these cases, the boronic acid moiety is in the scissile bond position. This also allows for a nucleophilic attack on the trigonal boronic acid and results in reversible covalent inhibition. The active site of proteases is defined based on the binding pocket for each amino acid residue. Starting from the scissile bond, it is defined as S_1, S_2, S_3, etc. to the left and S_1', S_2', S_3', etc. to the right. The corresponding inhibitor/substrate residues are defined as P_1, P_2, P_3, and P_1', P_2', and P_3', etc [49]. In designing boronic acid-based inhibitors, one can only take advantage of the binding pockets on one side of the scissile bond because of the need to preserve the free boronic acid. In some cases this could limit its selectivity or affinity.

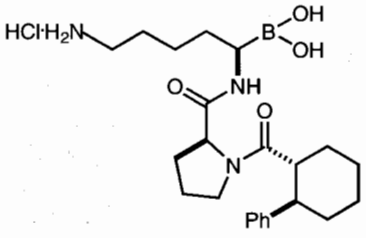
The very first examples were some simple boronic acid compounds [5, 6]. For example, phenylboronic acid and substituted phenylboronic acids were found to be strong competitive inhibitors of subtilisin and chymotrypsin [6]. More recently, boronic acids have been used for the synthesis of inhibitors against thrombin [50, 51], lactamases [52], dipeptidyl peptidases [53], and others [54, 55]. In this section, thrombin inhibitors will be used as examples. The rest will be summarized in a table at the end of the section.

Thrombin, as the final serine protease in the blood coagulation cascade, is a promising target for the development of anticoagulant agents. Therefore, there is a great deal of interest in the development of thrombin inhibitors. Fevig and co-workers at the former DuPont Merck Pharmaceuticals, Inc. demonstrated that boronic acid derivatives of peptides could be effective inhibitors of thrombin. Among these inhibitors, compound **8** (Figure 13.1) was reported to have a K_i of less than 1 nM [56]. As discussed above, the boronic acid occupies the scissile bond position with the remaining part of the molecule occupying either side of the scissile bond, but not both. Examination of the X-ray crystal structure of boropeptide **8** bound to thrombin showed that the 3-phenylpropionyl chain attached to the proline residue forms a favorable edge-to-face interaction, with the Trp-215 side-chain at the base of the S3

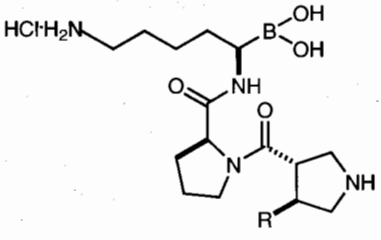


8 R = H (K_i = 0.80 nM)

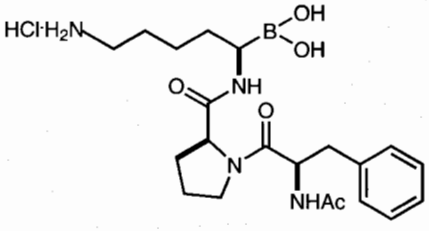
9 R = CF_3 (K_i = 0.78 nM)



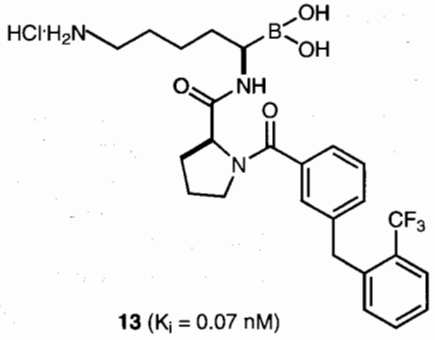
10 (K_i = 0.46 nM)



11 R = 3-$CF_3C_6H_4$ (K_i = 0.50 nM)



12 (K_i = 0.24 nM)



13 (K_i = 0.07 nM)

Figure 13.1 Boronic acid-based thrombin inhibitors (Part A).

specificity pocket of thrombin (Figure 13.2) [56]. To maximize this edge-to-face interaction, rigidified analogs of **8** and **9** were designed. In such a design, a cyclohexane ring (**10**) or a pyrrolidine ring (**11**) was used to hold the phenylpropionyl moiety in an orientation favorable for the interaction with the Trp-215 residue, as predicted by computer modeling studies based on the X-ray crystal structure. Both constrained analogs **10** and **11** showed a two-fold increase in potency relative to their unconstrained counterparts **8** and **9**, respectively. In a related effort to maximize the edge-to-face interaction with the Trp-215 side-chain, the P3 residue of **12**, a previously discovered inhibitor, was replaced by benzoic acid-derived residues. This afforded the extremely potent thrombin inhibitor **13**, which is about three-fold more potent than the lead compound (**9**) [57].

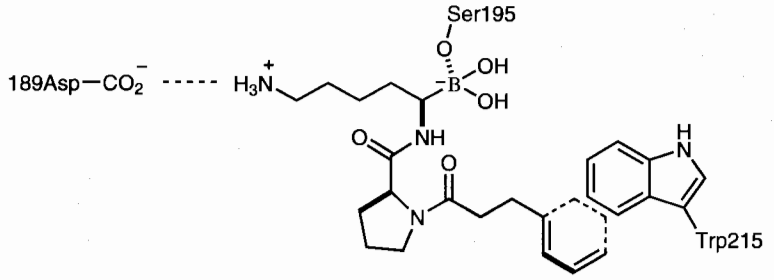
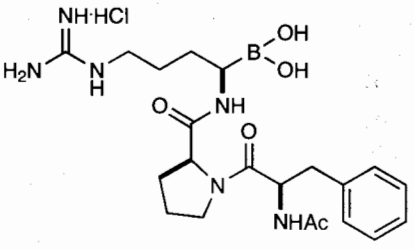


Figure 13.2 Binding of compound **8** to thrombin. Three key interactions are shown: (a) interaction with the amino side-chain of Asp-189 in the S1 specificity pocket; (b) tetrahedral complex formed between the hydroxyl group of Ser-195 and the boron atom of the inhibitor; (c) edge-to-face interaction of the 3-phenylpropionyl (P3) residue with Trp-215 located at the base of the S3 specificity pocket.

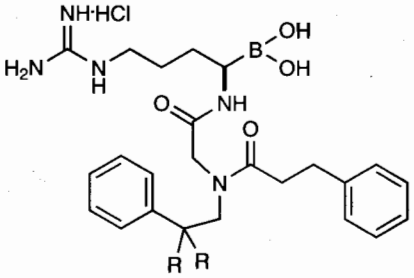
One important aspect of the structural studies is the affirmation that the Lewis acidity of the boron atom in a boronic acid does play an important role in the inhibition of a hydrolytic enzyme such as thrombin, as designed. For example, the active site serine hydroxyl group of thrombin is covalently linked to the boron atom in the enzyme–inhibitor (**8**) complex (Figure 13.2), converting the boron into the tetrahedral form, mimicking the somewhat tetrahedral transition state as intended. A separate structural study using a boronic acid-based inhibitor of α-lytic protease provides additional evidence that the boron atom participates in covalent binding with the active site nucleophile upon binding to a hydrolytic enzyme. In addition, the hydroxyl groups of the boronic acid moiety may be hydrogen-bonded to other functional groups, such as the histidine imidazole group and/or an active site water, to further stabilize the complex [58–60].

In an earlier and related study, DuP-714 (**14**, Figure 13.3) was identified as a very potent thrombin inhibitor (K_i of 0.07 nM) [50]. Animal studies indicated that DuP-714 caused a side effect that appears to be related to the undesirable inhibition of complement Factor I. To design inhibitors with minimal interaction with Factor I, it was important to analyze the difference in the binding requirements between Factor I and thrombin. However, the crystal structure of Factor I was not available. Therefore, the crystal structure of Factor Xa (fXa) was used, working on the assumption that the overall conformation of Factor I is similar to that of Factor Xa. Crystal structural analyses of the enzyme complexes with different inhibitors showed that there were very noticeable differences in the P2 pocket. Therefore, a series of β,β-dialkylphenethylglycine P2 analogs of DuP-714 (**14**) were designed and synthesized. These compounds, such as **15** and **16**, showed greater selectivity for thrombin over factor I and improved safety profile [61].

There have also been efforts in designing selective thrombin inhibitors by varying the P1 position. For example, incorporation of *m*-cyano-substituted phenylalanine boronic acid analogues into R-(D)Phe-Pro-OH dipeptides produced several highly effective thrombin inhibitors such as H-(D)Phe-Pro-boroPhe(*m*-CN)-OH [62]. The cyano group enhances binding by several orders of magnitude. Because of its struc-

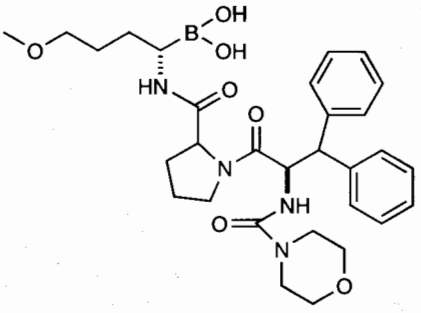


14, DuP 714
(K_i = 0.04 nM for thrombin, 9 nM for fXa)

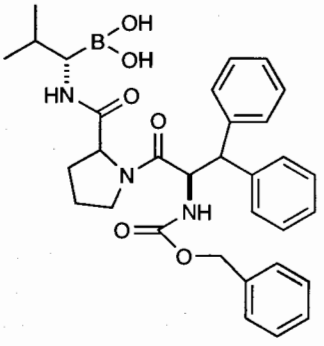


15 R = Me (K_i = 0.06 nM for thrombin, 99 nM for fXa)

16 R = -CH_2- (K_i =0.06 nM for thrombin, 46 nM for fXa)



17 (K_i = 3 nM)



18 (K_i = 20 nM)

Figure 13.3 Boronic acid-based thrombin inhibitors (Part B).

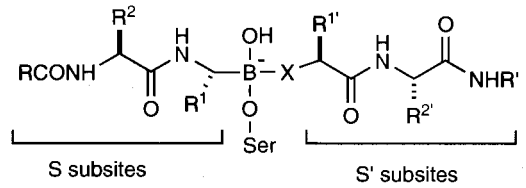
tural and functional similarities with thrombin, trypsin was used as a surrogate in the crystal structural studies. The trypsin-H-(D)Phe-Pro-boroPhe(*m*-CN)-OH (K_i = 0.48 nM) complex showed that the aromatic side-chain was bound in the P1 binding site and that the cyano group acted as a H-bond acceptor for the amide proton of the Gly-219. Among these studies, there was an interesting finding through the crystallographic analysis of the complexes of human α-thrombin (HαT) with peptide boronic acids (**17** and **18**) [63], i.e., the crystal structures showed that peptide boronic acids (**17** and **18**) lacking a positive charge at P1 had novel interactions with the S3 site of HαT.

13.2.2
Boronic acid–Nucleophile Complex Formed in the Enzyme Active Site as a way to Improve Potency and Selectivity

As discussed earlier, free boronic acids can only be used to bind to one side of the binding pocket of a protease, which does not allow for the maximal use of the active site to achieve the best affinity and specificity. Moreover, the reversible nature of boronic acid complex formation makes it hard to incorporate functional groups on

both sides of the boronic acid moiety. Efforts have been made to overcome this problem. One possible way to achieve this is to design a system that would form a complex in the enzyme active site using two components that can each recognize one side of the active site of the enzyme (Figure 13.4). There are two general approaches to this. First, one can design two inhibitors. The combined use of two inhibitors could lead to the formation of a complex in the active site (**19**), which has the potential to improve affinity and specificity. The second approach is to tether the two separate components together as one molecule. If an appropriate tethering unit is used, a favorable entropic factor may help in promoting the inhibitory complex formation (**20**) (Figure 13.4).

19



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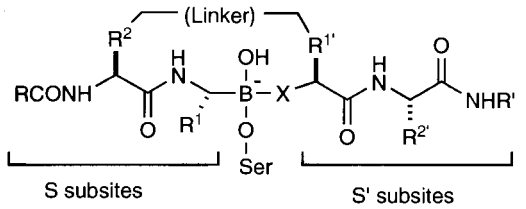
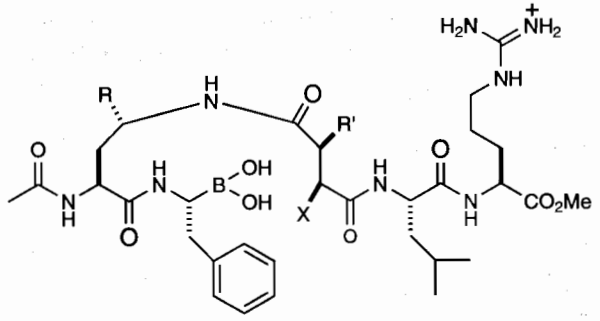


Figure 13.4 Proposed binding of serine protease in (a) a ternary complex with a boronic acid (**19**) and (b) with an intramolecular tetrahedral boronic acid adduct (**20**).

Peptidyl boronic acids **21**–**23** (Figure 13.5) were designed and synthesized to explore the possibility of forming a peptide boronate adduct in the serine protease active site that mimics the first tetrahedral intermediate in the peptide hydrolysis mechanism [64]. As discussed above, this design is intended to take advantage of an intramolecular process, hoping to overcome the inherent disadvantage of ternary adduct formation (Figure 13.4, **19**) by tethering P′ components to the peptidyl boronic acid (Figure 13.4, **20**). Consequently, the binding region could be extended to the S′ binding sites and large increases in the inhibition constants might be possible. The complex boronates thus prepared are potent inhibitors of α-chymotrypsin. However, the affinity of **21** is neither time- nor pH-dependent, which would be expected for a covalent inhibitor, and it only shows a moderate increase in affinity compared to compounds **24**–**26** (Figure 13.5) that cannot form a diester adduct. These results do not follow the predictions. The authors suggested that either boronate ester formation was not occurring, or that the energy derived from binding of the S′ binding fragment and boronate ester formation was not sufficient to offset the flexibility or binding characteristics of the linking group. Although this approach has not yielded positive results, the validity of the concept remains true and merits further studies. Of

course, one key to the success of this approach is the design of the appropriate tethering unit, which should (1) favor the intramolecular complexation and (2) possess functional groups for favorable interactions with the targeted enzyme.

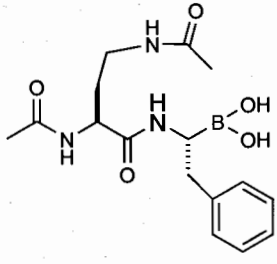


21 R = Me, R' = *t*-Bu, X = OH (K_i = 26 nM)

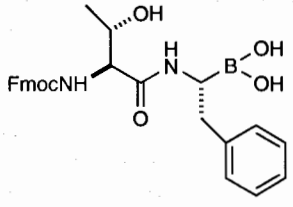
22 R = R' = H, X = NH_2 (K_i = 133 nM)

23 R = R' = H, X = OH (K_i = 68 nM)

24 R = R' = X = H (K_i = 114 nM)



25 (K_i = 356 nM)



26 (K_i = 219 nM)

Figure 13.5 Macrocyclic peptidyl boronic acids as potential chymotrypsin inhibitors.

13.2.3
Boronic Acids used for the Binding of the Non-scissile Position

Often when boronic acids are used as inhibitors of hydrolytic enzymes, the boronic acid moiety is at the reaction center, mimicking the transition state of the hydrolytic processes. Boronic acids can also be used to simply promote binding. In such cases, the boronic acid moiety is at a remote site away from the reaction center, and is only involved in the binding. Along this line, boronic acids have been used for the preparation of argininase and NO synthase inhibitors.

Arginase plays a crucial role in the regulation of diverse metabolic pathways such as ureagenesis and nitric oxide biosynthesis. Recently, the synthesis and evaluation of nonreactive arginine analogues as possible enzyme inhibitors or receptor antago-

nists have attracted much attention. The X-ray crystal structure of rat liver arginase shows that the trimeric metalloenzyme contains a binuclear manganese cluster in the active site of each subunit required for maximal catalytic activity [65]. Using the X-ray crystal structure of the ternary arginase-ornithine-borate complex in which the manganese-bridging solvent molecule of the native enzyme is displaced by an oxygen of the tetrahedral borate anion, the first boronic acid arginine analogue, (2*S*)-amino-6-boronohexanoic acid (ABH), was designed, synthesized and evaluated as an arginase inhibitor [66]. The inhibitory activity of ABH against Mn^{2+}-arginase was evaluated using a radioactive assay to yield an IC_{50} of 0.8 μM. The crystal structure of the complex between arginase and ABH was also determined [67]. ABH binds as the tetrahedral boronate anion that mimics the intermediate of a metal-activated hydroxide mechanism. The tight binding and high specificity of ABH allow for further studies on the physiological role of arginase in regulating the NO-dependent biological processes. Significant enhancement of nonadrenergic, noncholinergic nerve-mediated relaxation of penile corpus cavernosum smooth muscle was observed with ABH and these results suggested that arginase inhibition sustained L-arginine concentrations for NO synthase activity. Therefore, human penile arginase is a potential target for therapeutic intervention in the treatment of erectile dysfunction.

Another similar boronic acid-based arginine analogue (*S*)-(2-boronoethyl)- L-cysteine (BEC) (**27**) (Figure 13.6), in which a sulfur atom was introduced, was also designed and synthesized [68]. Biological test showed it as a slow-binding competitive inhibitor of arginase with a K_i of 0.4–0.6 μM. The X-ray crystal structure of the arginase-BEC complex was also determined, revealing that the binding mode also mimics the tetrahedral intermediate in the arginine hydrolysis reaction as ABH does. Similarly, BEC also causes significant enhancement of NO-dependent smooth muscle relaxation in human penile corpus cavernosum tissue. Further biological studies [69] demonstrated that both ABH and BEC are classical, competitive inhibitors of human type II arginase at pH 7.5 with K_is of 0.25 and 0.31 μM, respectively. However, at pH 9.5, both were found to be slow-binding inhibitors of the enzyme with K_is of 8.5 and 30 nM, respectively. The apparent pK_a of the boronic moiety is ~8.5 [3]. Therefore, the compounds are expected to exist in the tetrahedral form at pH 9.5 and the trigonal form at pH 7.5. This could help to explain the enhanced potency at pH 9.5. Further determination of the X-ray structure of human arginase II complexed with BEC was conducted [70], which also shows the same binding mode with a metal-activated hydroxide mechanism. Hemodynamic experiments in vivo suggest that the extrahepatic arginase plays a role in both male and female sexual arousal. Accordingly, arginase II is a potential target for the treatment of male and female sexual arousal disorders.

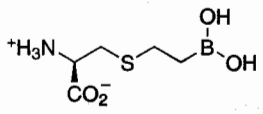


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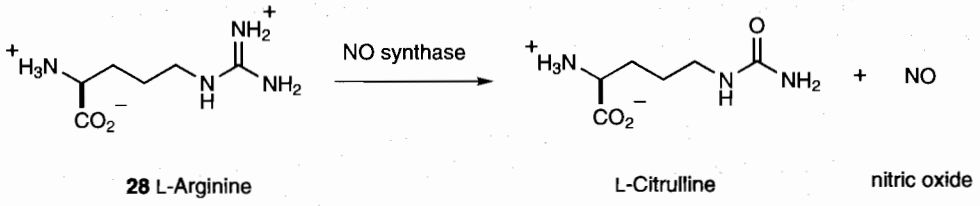
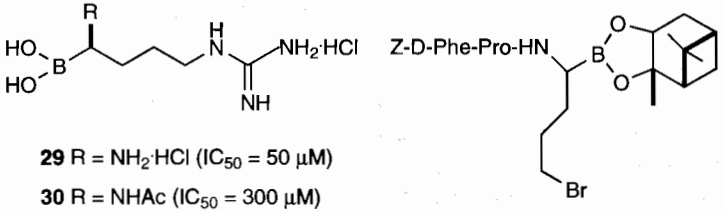
Figure 13.6 Structure of (*S*)-(2-boronoethyl)-L-cysteine (BEC, **27**).



28 L-Arginine L-Citrulline nitric oxide

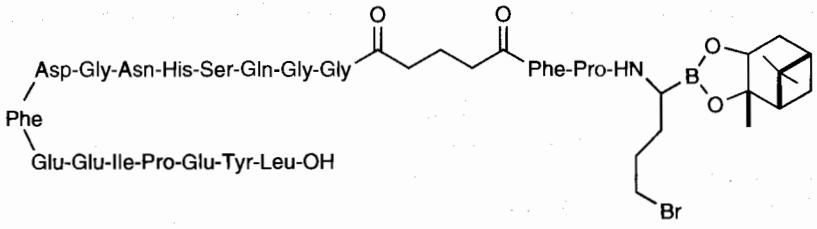
Scheme 13.4 Illustration of NO biosynthesis.

Nitric oxide (NO) displays potent activities in the cardiovascular system as well as in the central and peripheral nervous systems. NO and its co-product L-citrulline are produced by the oxidation of L-arginine (**28**) by nitric oxide synthase (NOS) (Scheme 13.4). Selective modulation of NO biosynthesis offers the opportunity for therapeutic intervention of neurodegenerative diseases, among others. Based on the mechanism proposed for NO biosynthesis, two boronic acid analogues (**29** and **30**, Figure 13.7) of

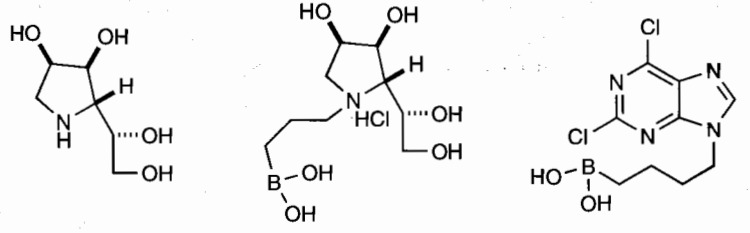


29 R = NH_2·HCl (IC_{50} = 50 μM)
30 R = NHAc (IC_{50} = 300 μM)

31a (K_i = 8 nM)



31 (K_i = 0.6 nM)



32 (K_i = 0.12 mM) **33** (K_i = 0.2 mM) **34** (EC_{50} = 0.99 μM)

Figure 13.7 Boronic acids and esters as inhibitors of nitric oxide synthase, glycosidases, thrombin, and HIV protease.

L-arginine were designed and synthesized as potential substrates or inhibitors of nitric oxide synthase [71]. The abilities of the boro-L-arginine **29** and **30** to generate NO and to inhibit [^{3}H]-L-citrulline formation from [^{3}H]-L-arginine were investigated using purified recombinant neuronal and inducible NOSs. The N^{α}-acetyl derivative **30** did not lead to any significant NO formation and poorly inhibited L-citrulline formation ($IC_{50} > 500$ μM). However, the unprotected boro-L-arginine **29** selectively inhibited L-citrulline formation catalyzed by the inducible NOS ($IC_{50} = 50$ μM) compared to the neuronal isoform ($IC_{50} = 300$ μM). These results demonstrated the feasibility of using boronic acid compounds for the inhibition of this enzyme and the strict substrate specificity of NOSs.

13.2.4
Boronic Esters as Enzyme Inhibitors

As discussed in the Introduction, boronic ester formation is a readily reversible process. Therefore, most of the inhibitors are used in their free acid form. However, if one uses a diol that can form a very tight covalent adduct with a boronic acid, one can make an ester inhibitor that is stable enough to hydrolysis on the time scale needed for the inhibitory activities.

Pinanediol esters of boronic acid are stable to trifluoroacetic acid exposure over a 2 h period [72]. This property makes pinanediol esters ideal for solid-phase peptide synthesis to generate boronic acid libraries. Based on the known potent inhibition effect of hirudin on thrombin, a peptide boronate as thrombin inhibitor was designed and synthesized using Fmoc solid-phase chemistry and pinanediol protected aminoboronates [72]. By conjugating a boronic acid moiety with a hirudin-based recognition moiety, compound **31** (Figure 13.7) was synthesized and shown to have a very high affinity for the target enzyme ($K_i = 0.6$ nM). It has a ten-fold higher potency relative to the corresponding non-hirudin-containing portion compound **31a** or the mixture of non-covalently linked units.

Pinacol is the other diol suitable for preparation of boronic ester inhibitors. In a separate study, a pinacol-protected boronic ester of Ac-Thr-Glu-Leu-Lys-Glu-boroLeu-OH·TFA (DPC-AB9144-00) was designed and synthesized as a boron-modified peptidyl mimetic of the bovine viral diarrhea virus (BVDV) NS4A/NS4B cleavage site and shown to be an efficient inhibitor of the BVDV NS3 protease [55].

13.2.5
Boronic Acids as Inhibitors of Glycosidases

Glycosidase enzymes that exist on cell surface are involved in many important biological processes, such as viral infection and tumor metastasis [73]. The development of new inhibitors of glycosidases is an attractive strategy for developing new anti-tumor, antiviral and anti-diabetic agents [74]. Iminosugars are naturally-occurring glycosidase inhibitors [75], which become protonated in the active site and serve as mimics of the electron-deficient transition state involved in glycoside hydrolysis. A series of boronic acid-containing iminosugars was synthesized and evaluated as inhibitors

of glycosidases [76]. One such compound (**33**) was shown to inhibit β-galactosidase with a $K_i = 0.2$ mM. However, interestingly, the "parent" compound (**32**), which does not have the boronic acid moiety, is an α-mannosidase inhibitor ($K_i = 0.12$ mM). It is unclear how the addition of a boronic acid imparts such selective inhibitory activities in this series. More structural studies are needed to understand this in detail.

13.2.6
Boronic Acids as Agents Targeting the Human Immunodeficiency Virus

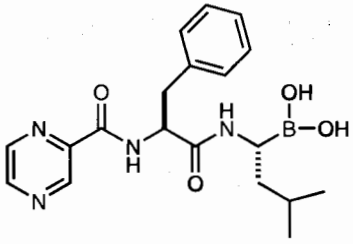
The human immunodeficiency virus, HIV-1, is generally accepted to be responsible for AIDS. Many and various nucleoside analogues have been developed as antiviral and anti-tumor agents. Along this line, a series of nucleosides containing the boronic acid group has been designed and synthesized as potential antiviral agents, especially targeting the human immunodeficiency virus [77]. Among these nucleoside derivatives, compound **34** exhibited an EC_{50} of 0.99 μM in an HIV-1 syncytial plaque reduction assay.

HIV-1 protease is involved in the production of infectious virions of HIV-1. Inhibition of HIV-1 protease provides an effective way to develop new agents for therapy of HIV-1. Taking HIV-1 protease as the target, a series of boronated tetrapeptides with the carboxy moiety of phenylalanine replaced by a boronic acid group was designed as substrate analogs that mimic the C-terminal part of the scissile bond (Phe-Pro) within the gag-pol polyprotein [78, 79]. Among the boronic acids synthesized, Ac-Thr-Leu-Asn-boroPhe inhibited HIV-1 protease with a K_i of 5 μM, whereas the corresponding non-boronated compound was inactive at concentrations up to 400 μM. These results indicate the significance of boronation in enzyme inhibition. Moreover, these boronic acids were also able to inhibit an HIV-1 protease variant that is resistant to several HIV-1 protease inhibitors. Although a K_i in the low micromolar range is far from being potent enough for drug development, the importance of the boronic acid group in helping to improve selectivity and potency is well demonstrated in these examples.

13.2.7
Bortezomib as a Proteasome Inhibitor for Cancer Therapy: A Successful Example

The proteasome is a eukaryotic cytoplasmic protease complex that has several distinct catalytic sites. It plays a major role in cellular pathways for the breakdown and processing of proteins to peptides and amino acids [80]. Unsurprisingly, defects of various components of this enzyme result in a range of human diseases, including Angelman's syndrome, cervical cancer, and Alzheimer's disease. As a result, these components provide attractive targets for therapeutic intervention. The proteasome showing chymotrypsin-like activity was reported to be the first member of a newly identified class of threonine proteases. Some selective and novel dipeptide aldehyde inhibitors of the chymotrypsin-like activity of the proteasome complex have been reported [81]. Based on the dipeptide aldehyde inhibitors, a series of tri- and di-peptidyl boronic acid analogues were designed [82] by the replacement of the corresponding

aldehyde function of previously reported proteasome inhibitors [83]. Bioassay of these compounds revealed that the incorporation of a boronic acid moiety in this series resulted in dramatically enhanced potency compared to the corresponding peptidyl aldehyde compounds. This enhancement is presumed to be due to the formation of a stable tetrahedral boronic acid intermediate with the *N*-terminal threonine residue of the catalytically active proteasome β-subunits, as has been demonstrated with boronic acid-based thrombin inhibitors. Among the compounds prepared, bortezomib (Velcade; PS-341, Figure 13.8) inhibits the 20S proteasome involved in the degradation of intracellular proteins, including those that affect cell cycle regulation in mammalian cells, and offers the advantages of low molecular weight and easy synthesis. Furthermore, it exhibited extremely high selectivity for the proteasome over common serine proteases. This selectivity is due to the unique structural features of bortezomib. As a dipeptide, bortezomib does not fulfill the requirements of enzymes such as chymotrypsin and elastase for the S3 and S4 binding pockets for optimal activity. The P1 position of this dipeptide boronic acid with a leucine residue does not match the preference of thrombin for a basic residue at that position. All these features made bortezomib very promising as a potential therapeutic for the treatment of cancer and inflammatory diseases.



Bortezomib (Velcade, PS-341)

Figure 13.8 Structure of bortezomib (Velcade; PS-341).

Many studies have been conducted aimed at developing bortezomib as a new agent in cancer therapy. After a Phase II studies in a total of 256 patients, accelerated approval of bortezomib was granted by the US Food and Drug Administration in early 2003 as a single agent for the treatment of multiple myeloma, a bone marrow cancer that affects two to three people per 100 000 [84], in patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy [31]. Therefore, bortezomib represents the first FDA-approved boronic acid agents for clinical use. As an extremely highly selective inhibitor for the proteasome over common serine proteases [85], bortezomib also demonstrates the concept that proteasome could be used as a target for cancer therapy [38]. Furthermore, bortezomib is being evaluated for lung cancer [86] and in combination therapies [29, 84, 86, 87]. It is expected that the successful discovery of bortezomib will stimulate more interest in the development of boronic acid-based inhibitors.

13.2.8 Others

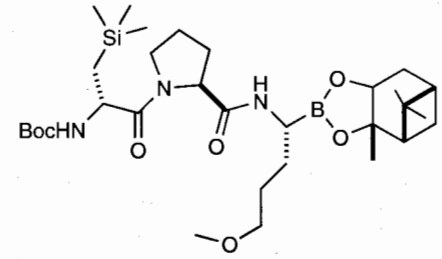
Numerous examples of boronic acid inhibitors have been reported in the literature. However, their basic design principles follow one of those described above. Therefore, some of the more recent examples are summarized in Table 13.1 and Figures 13.9 without a detailed discussion for each.

Table 13.1 Other representative boronic acids reported in the literature after 1996.

Compound	Enzyme	K_i (nM)	Reference
35	Thrombin	8.4	88
36	Thrombin	2.5	88
37	Factor Xa	1.1	89
D-[1-Acetamido-2-(1-naphthyl)ethyl]boronic acid	Subtilisin Chymotrypsin	– 127	90, 91
MeOSuc-Ala-Ala-Pro-boroPheOH	Subtilisin E Chymotrypsin α-Lytic protease	2.5 0.4 –	92–94
2,4-Dichlorophenylboronic acid	Chemically modified mutants of subtilisin	–	95, 96
p-Boronic acid benzophenone	Chemically modified mutants of subtilisin	–	97
3-Nitrophenylboronic acid	Prostate specific antigen	–	98
Ac-Ala-Lys-boroArgOH	Kex2	–	99
MeOSu-Ala-Ala-Pro-boroValOH	Pancreatic elastase Leucocyte elastase α-lytic protease	0.25 0.57 6.4	100, 101
Boc-Ala-Pro-boroValOH	Pancreatic elastase Leucocyte elastase α-lytic protease	0.32 – 0.35	100, 101
Pro-boroProOH	Dipeptidyl amino peptidase type IV (DP IV)	0.016	102–104
38	TME-1 β-lactamase	110	105
39	TME-1 β-lactamase	13	106
40	TME-1 β-lactamase	5.9	106
Benzo[*b*]thiophene-2-boronic acid	AmpC β-lactamase	27	107, 108
3-Iodoacetamidophenylboronic acid	908R class C β-lactamase	–	109
41	AmpC β-lactamase	20	110, 111
42	AmpC β-lactamase	83	112, 113
43	AmpC β-lactamase TME-1 β-lactamase	1 64	114, 115
45	Hepatitis C virus (HCV) NS3 protease	80	54
46	HCV NS3 protease	80	54
47	HCV NS3 protease	1600	116
48	HCV NS3 protease	2	117
49	HCV NS3 protease	–	118
Ac-Asp-Glu-Val-Val-Pro-boroArgOH	HCV NS3 protease	13	119

Table 13.1 Continued.

Compound	Enzyme	K_i (nM)	Reference
50	Dipeptidyl peptidase IV	–	120
51	Dipeptidyl peptidase IV	–	120
Val-boroProOH	Dipeptidyl peptidase IV	–	121, 122
	Fibroblast activation protein	–	
44	Proteasome	8	123
Bz-Phe-boroLeuOH	Proteasome	17	124
52	Cysteine protease	–	125
γ-BoroGluOH	γ-Glutamyl transpeptidase	17	126–129
	Glu-tRNA amidotransferase	100(IC_{50})	
γ-Glu-Leu-boroGlyOH	Glutathionylspermidine synthetase/amidase	17000(IC_{50})	130
Boc-Lys(Cbz)-D-boroAla-pinanediol	Penicillin-binding protein	370	131
Phenylboronic acid	Rice bran lipase	1700	132



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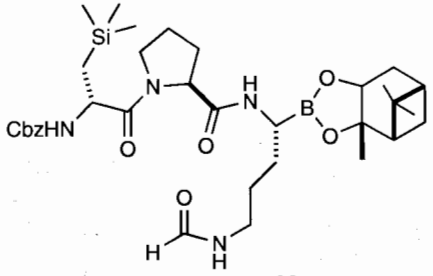

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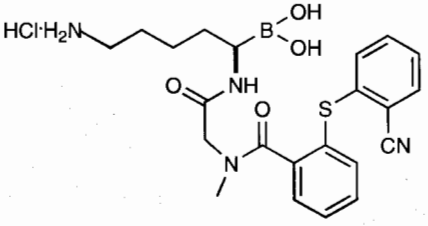

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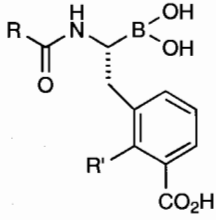
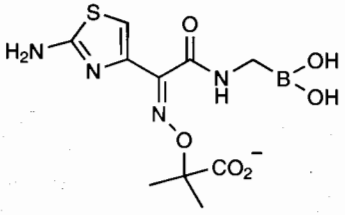


38 R = Me, R' = H

39 R = Me, R' = OH

40 R = $PhCH_2$, R' = H

Figure 13.9 Boronic acid-based enzyme inhibitors listed in Table 13.1.



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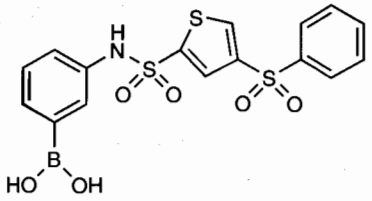

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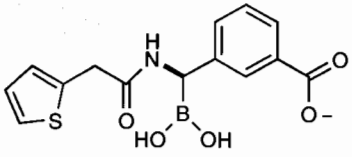

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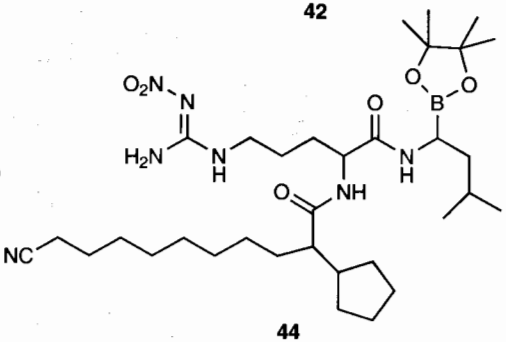

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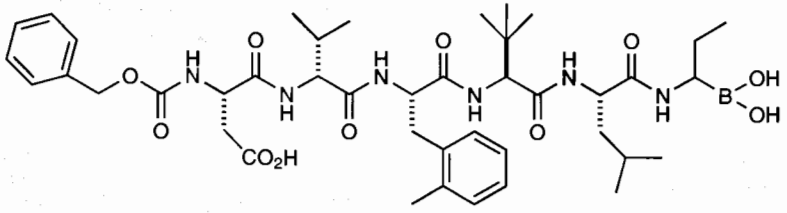

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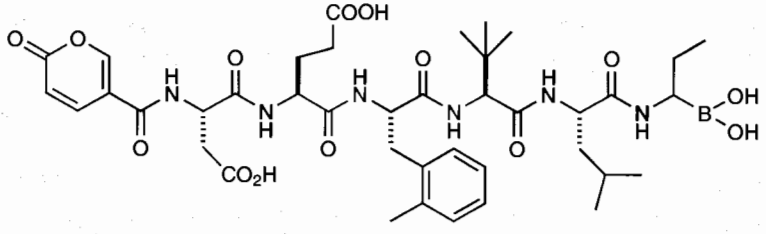

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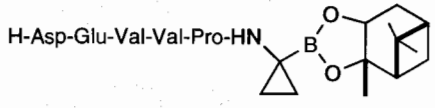

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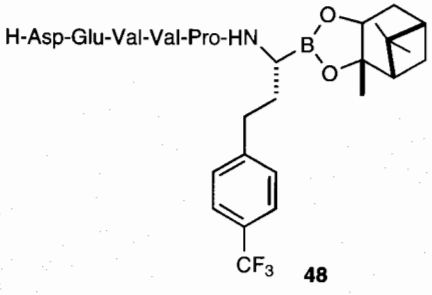

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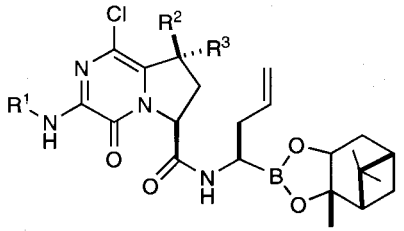
Figure 13.9 Continued



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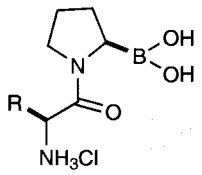

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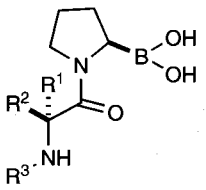

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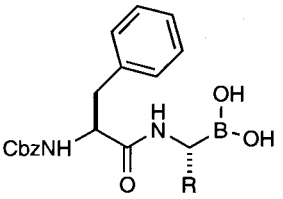

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Figure 13.9 Continued

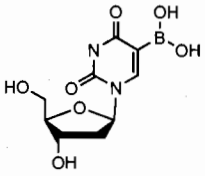
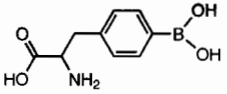
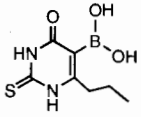
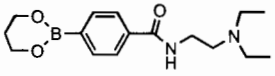
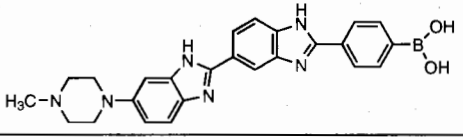
13.3
Boronic Acid Compounds as Boron Neutron Capture Therapy (BNCT) Agents

In addition to being used as enzyme inhibitors, boron compounds can also be used in boron neutron capture therapy (BNCT), which was first proposed in 1936 [27]. BNCT is based on the unique ability of boron-10 to transmute into lithium and emit α-particles upon irradiation with soft neutrons. Because α-particles are very damaging and only travel a very short distance, they are ideal candidates for localized cancer radiation therapy [28]. Successful application of BNCT requires the development of boron compounds that specifically deliver substantial quantities of ^{10}B to the target cells at very high concentrations [133–136].

Critical to the development of BNCT is the synthesis of boron-containing compounds that selectively target tumor cells. Numerous boron-containing compounds have been synthesized and tested [9]. Among them are nucleoside-based (**53**) [137–139], amino acid-based (54) [140–145], and cyclic thiourea-based boronic acids (**55**) [146], and a boronated benzamide (**56**) [147] (Table 13.2). The idea is that such compounds can be enriched selectively in rapidly growing tumor cells, which tend to have a higher demand on nutrients. In addition, there have also been efforts in incorporating the boronic acid moiety into DNA binders (**57**) aimed at targeting the rapidly proliferating tumor cells (Table 13.2) [148]. Although many of these boronic acids tested showed certain selectivity for tumor, they generally do not deliver high enough concentrations of B-10 for BNCT [28]. The current trend is to use boron clusters, which has little to do with boronic acids, for the delivery of high concentrations of B-

10 for BNCT [28]. The chemistry thus needed to develop effective BNCT agents is beyond the scope of this chapter.

Table 13.2 Boronic acid-based compounds as potential BNCT agents.

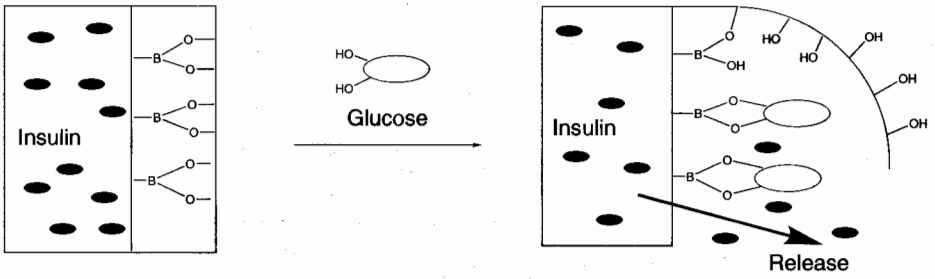
Compound number and references	Compound type	Structure
53 [137–139]	Nucleoside-based	
54 [140–145]	Amino acid-based	
55 [146]	Cyclic thiourea-based	
56 [147]	Boronated benzamide	
57 [148]	DNA binders	

13.4 Boronic Acid Compounds as Drug (Insulin) Delivery Devices and for *In Vivo* Glucose Imaging

Another unique property of boronic acids that can be explored for the development of biological applications is the tight binding between boronic acids (**3** and **4**, Schemes 13.2 and 13.3) and diol-containing compounds such as carbohydrates. This binding is through the reversible formation of boronic/boronate esters with vicinal diols (**7**) (Schemes 13.2 and 13.3) [3, 18, 149]. Such properties have been used to develop polymers that respond to glucose concentration by changing their permeability for proteins such as insulin [150–154]. One of the major obstacles in the management of diabetes, particularly type I diabetes, is the lack of continuous and feed-back

controlled insulin release systems [24]. Therefore, there is a great deal of interest in the development of systems that allow for the release of insulin based on glucose concentration. Conceivably, this kind of intelligent insulin release system can be achieved through the use of polymers that can change properties and permeabilities in response to changes in glucose concentrations [155, 156].

Along this line, boronic acid-based polymer complexes are sensitive to glucose as a potential insulin delivery system, presumably due to the competitive binding of glucose to boronic acids, which disrupts the boronic acid–diol complex network within the polymer matrix (Scheme 13.5) [157]. In one study, the phenylboronic acid (PBA) moiety was attached to poly(*N*-vinyl-2-pyrrolidone) (NVP) to form poly(NVP-co-PBA) (**60**) (Figure 13.10). Poly(vinyl alcohol) (PVA) was chosen as a complex partner because it can form a reversible complex with boronic acid moieties. Insulin was loaded into a polymer gel formed by the PVA/poly (NVP-co-PBA) complex (**58**). In the absence of glucose, the gel forms a tight, impermeable layer separating insulin from the outside environment (Scheme 13.5). However, in the presence of glucose, exchange reactions can happen due to the higher affinity of glucose for boronic acid than the poly(vinyl alcohol). Therefore, glucose can diffuse through the polymer gel and exchange with the PVA-boronate complex through the formation of a more stable glucose-boronate complex (**59**). This eventually leads to the formation of a glucose-boronate complex that changes the polymer from the gel state to a solution state, which facilitates the release of insulin from the polymer complex. Such a feed-back controlled system has the potential to be used for the construction of a reservoir type of depot for the maintenance of insulin concentration based on glucose levels.



58: closed, non-permeable form

59: open, permeable form

Scheme 13.5 A glucose-sensitive insulin release system using boronic acid polymer complexes (**58**).

During the last decade, much effort has been directed to improving the properties of such boronic acid-based polymers by changing their composition. An amine-containing phenylboronic acid gel has been reported to release insulin in a glucose-responsive fashion at physiological pH [158]. The amino group in the PBA gel beads strongly affects the gluconated insulin (G-ins) release due to the enhanced stability of the boronic acid complex with a diol in the presence of an amine. An improved type of glucose-sensitive polymer gel was found to be applicable to the on-off regulation of insulin release [159]. The major component of the gel was poly(*N*-isopropylacry-

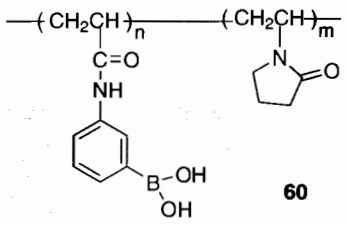


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Figure 13.10 Phenylboronic acid-based polymers for controlled insulin release.

lamide) (PNIPAAm) that was derivatized with certain a ratio of phenylboronic acid as the glucose-sensitive moiety (**60**). Glucose addition significantly changed the gel swelling properties. As a result, an on-off regulation of insulin release from the gel was achieved.

Boronic acid compounds could also potentially be used for in vivo glucose imaging. A EuDOTA-tetraamide ligand with bis(phenylboronate) arms (**61**) has been used as paramagnetic chemical exchange saturation transfer (CEST) agent for imaging glucose by MRI (magnetic resonance imaging) (Figure 13.11) [160]. The binding between boronic acid and glucose alters the water exchange between a Eu^{3+}-bound water molecule and bulk water. This prototype CEST agent is sensitive to changes in glucose concentration over a range of physiological interest (5–10 mM). This was said to be useful for mapping the distribution of glucose in tissue by MRI using the bulk water proton as antenna. However, this method is unlikely to be used for the routine determination of blood glucose concentration for diabetic patients.

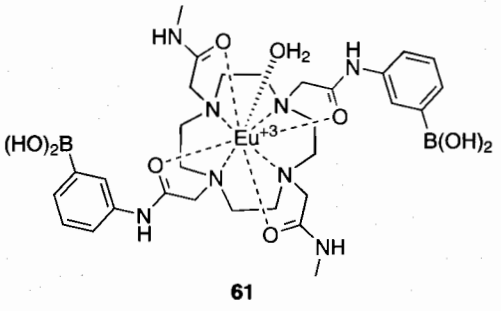

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Figure 13.11 EuDOTA-tetraamide ligand with bis(phenylboronate) arms (**61**) for imaging glucose by MRI.

13.5
Cell Surface Carbohydrate Recognition by Artificial Lectins – Boronolectins

Cell surface carbohydrate structures, as part of glycosylated proteins and lipids, form characteristic signatures of different cell types [161, 162]. Certain cell surface carbohydrates, such as sialyl Lewis X (sLex) (**62**) (Figure 13.12), sialyl Lewis a, Lewis Y, and Lewis X, are associated with the development and progression of many types of cancers [163–166]. For instance, over-expression of sLex containing mucins is an important sign for the development of gastrointestinal, pancreatic, and breast cancer. Therefore, the development of sensors that recognize sLex could help the diagnosis and early detection of cancers [167, 168]. Since the recognition of cell surface carbohydrates by these sensors mimics the action of lectins, these sensors are essentially artificial lectins. Because they all contain the boronic acid moiety, these sensors can also be termed as boronolectins. Boronolectins can also be considered as antibody mimics that can be used as vectors for targeted drug delivery. During the last few years, the Wang laboratory has devoted a significant effort to developing such fluorescent boronolectins that show fluorescence intensity increases upon binding with the cell surface saccharides. Although the fluorescence intensity changes are not essential for certain applications, the fluorescent property makes the screening much easier.

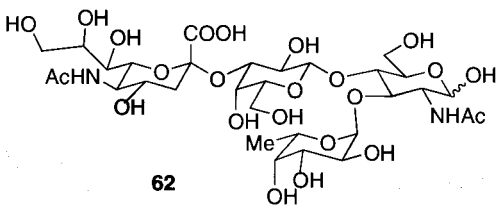

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Figure 13.12 Sialyl Lewis X (sLex) tetrasaccharide.

The design of fluorescent boronolectins that recognize unique saccharide biomarkers relies on three major components: the strong interaction between the boronic acid moiety, the availability of fluorescent boronic acids that provide a change (preferably increase) in fluorescence upon diol binding, and the construction of the appropriate three-dimensional scaffold. When the cell surface carbohydrate recognition project was at the initial phase in the Wang laboratory, the best available fluorescent reporter compound (**63**) was a system developed by the Shinkai group (Figure 13.13) [169]. This system shows a very significant fluorescence intensity increase upon binding with a diol, although the detailed mechanism through which this occurs is not, as originally proposed, due to the B–N bond formation [169–171].

One of the earliest targets was sLex, which again is correlated with the development of colorectal and liver cancer [172, 173]. sLex has several pairs of diols that can be recognized by the boronic acid moiety. It is conceivable that a compound that has two boronic acid moieties with the appropriate spacing and orientation that are complementary to that of the diol pairs on sLex could display specific binding with sLex. In

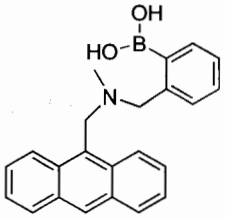

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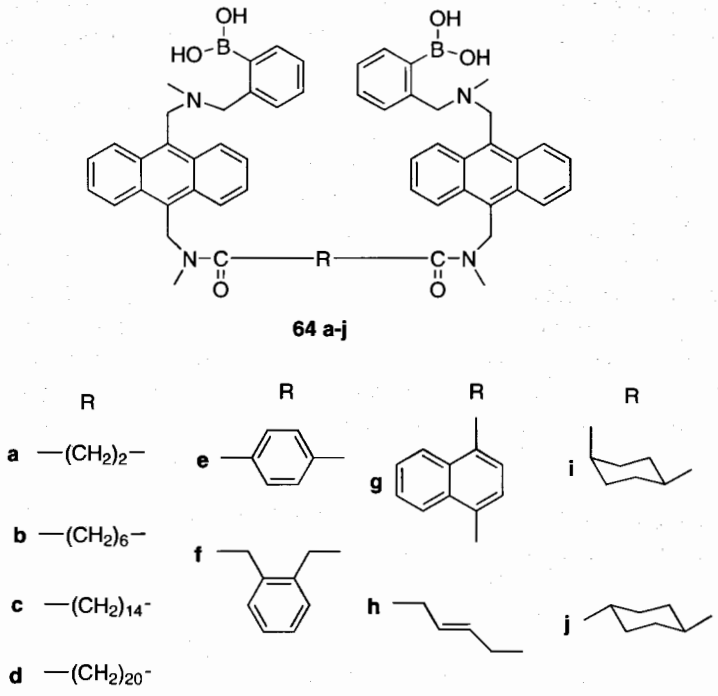
Figure 13.13 Anthracene-based boronic acid fluorescent reporter compound.

searching for the appropriate 3D scaffold for the recognition of sLex, various linkers tethering two anthracene boronic acid units were sampled (Figure 13.14) [25, 26]. In screening for their binding with these target carbohydrates, these compounds (**64a–j**) showed varying degrees of fluorescence intensity changes upon addition of a carbohydrate, indicating varying degrees of affinity for the carbohydrate. Among them, **64e** showed the greatest fluorescence intensity change upon addition of sLex. This compound was then tested for its ability to fluorescently label cells that express the target saccharide, sLex [25, 26]. Figure 13.15 shows that sensor **64e** can fluorescently label sLex-expressing HEPG2 cells, but not the non-expressing COS7 cells at 1 and 5 μM concentrations. This sensor was also able to label tumor tissues known to have high



64 a-j

Figure 13.14 Diboronic acid compounds as potential boronolectins for recognition of cell surface carbohydrates.

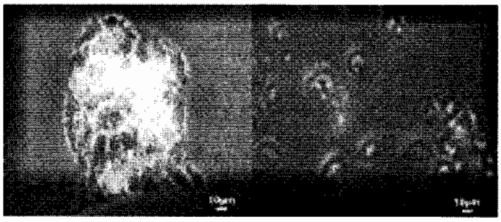
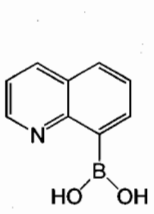


Figure 13.15 Fluorescent labeling studies of sLex expressing HEPG2 cells (left) and non-expressing COS7 cells (right) with compound **64e** (1 μM).

levels of surface sLex. Such results unambiguously demonstrate the proof of concept of using fluorescent boronolectins for the fluorescent labeling of cells expressing the target saccharides.

Notably, experiments with neuraminidases and fucosidase, which cleave the sialic acid and fucose portions of sLex, respectively, have demonstrated that both the sialic acid and fucose moieties are required for binding. This is consistent with the two-point binding model as designed. Although one would not expect either sialic acid or fucose in its pyranose form to bind tightly with a monoboronic acid, the proper positioning of the two boronic acid moieties likely results in a synergistic effect.

Compounds such as **64e** have the potential to be used for the development of platform technologies that integrate diagnosis, sensing, drug delivery (intervention), and post-therapy monitoring into one system. However, for in vivo applications, one has to be concerned about the properties of the boronolectins in terms of solubility, permeability, stability, metabolic properties, and toxicity. The anthracene moiety present in the **64e** makes it an unlikely candidate for further clinical development due to its high hydrophobicity and a lack of metabolic stability. To address this problem, the Wang laboratory has also undertaken an effort to design and synthesize fluorescent boronic acid reporter compounds that show large fluorescence intensity changes upon binding, are water soluble, and lack the known toxicity problems associated with anthracene. Along this line, several fluorescent boronic acid compounds, such as **65** and **66** (Figure 13.16), have been developed that possess such desirable physicochemical properties [20, 21, 174]. For example, 8-quinoline boronic acid (**65**, 8-QBA) shows an unprecedented 40-fold fluorescence intensity change upon binding to a saccharide such as fructose, and is water-soluble [20]. Such a new generation of fluorescent reporters can be used for the development of clinically useful fluorescent boronolectins that recognize unique cell-surface carbohydrate markers. Another important consideration in the synthesis of boronolectins or fluorescent boronolectins is the ability to synthesize a large number of compounds with high structural diversity. Recently, the Hall group has published a modular approach to the synthesis of such boronic acid compounds, which should help to advance this field [175].



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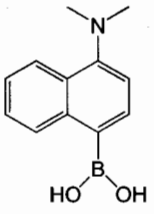

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Figure 13.16 Water-soluble fluorescent reporter compounds.

13.6 Conclusions

Due to their unique electronic structures, boronic acid compounds can be used for the development of enzyme inhibitors, BNCT, feed-back controlled drug release systems, and artificial lectins (boronolectins) that recognize unique cell surface carbohydrate biomarkers. There are especially high levels of activities in using boronic acids for the development of enzyme inhibitors and boronolectins for the recognition of cell-surface biomarkers. The recent approval of bortezomib by the US Food and Drug Administration for the treatment of multiple myeloma is both an affirmation of the biological utilities of boronic acid compounds and a stimulus for the further development of new boronic acid-based pharmaceutical agents. Many reports of new biologically active boronic acids and their mechanistic examinations are coming out even as this chapter is being finalized [26, 176–186]. This is a very good indication that more and more people have realized the unique and important roles that boronic acid compounds can play in developing new biologically active agents.

Acknowledgments

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